Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Lactic acid isomers

Evaluation statement

14 January 2022

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AICIS evaluation statement

Subject of the evaluation

Lactic acid isomers

Chemicals in this evaluation

Name	CAS registry number
Propanoic acid, 2-hydroxy-	50-21-5
Propanoic acid, 2-hydroxy-, (S)-	79-33-4
Propanoic acid, 2-hydroxy-, (2R)-	10326-41-7

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health.

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.

These chemicals have been assessed as a group as they are structurally very similar and share the same use patterns.

Summary of evaluation

Summary of introduction, use and end use

Lactic acid isomers have reported uses in cosmetics in Australia at concentrations up to 30%.

Based on international use information, some of the chemicals in this group are used in a range of cosmetic and personal care products, including in chemical skin peels or exfoliating products (up to 30% in salon peels), deodorants (up to 1.7% in oral hygiene products and baby care products.

Some of the chemicals in this group have various domestic uses, including in laundry dishwashing and cleaning products (up to 18%) and air freshener products.

The chemicals in this group have various site limited uses, including in the manufacture of chemicals and materials.

Some of chemicals in this group have non-industrial uses including in therapeutic goods, agricultural products, veterinary products and foods in Australia.

Human health

Summary of health hazards

The critical health effects for risk categorisation are local effects including skin irritation and eye damage.

L-lactic acid is biologically active and involved in cellular metabolism. It is produced in various cells throughout the body including muscle cells, brain cells and red blood cells. Mixed and D-lactic acid are widely produced and used in the food industry. Systemic toxicity of lactic acid isomers is therefore not likely, and available data are consistent with this expectation.

Based on the limited available data for L-lactic acid (CAS No. 79-33-4), the chemicals in this group are expected to have low acute oral toxicity (median lethal dose (LD50) = 3543 mg/kg body weight (bw) in female rats and 4936 mg/kg bw in male rats), low acute dermal toxicity (LD50 >2000 mg/kg bw in rabbits), and low acute inhalation toxicity (median lethal concentration (LC50) >7.94 mg/L; 4 hours in rats).

Based on the available data for L-lactic acid, the chemicals in this group are expected to be skin irritants. In an in vivo skin irritation study conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 404, L-lactic acid was considered to be severely irritating and corrosive to rabbit skin. In other skin irritation studies, L-lactic acid was found to be slightly irritating to guinea pig skin, but not irritating to pig skin. The data are sufficient to warrant hazard classification as skin irritants.

Based on the limited available data for L-lactic acid, the chemicals in this group are expected to cause serious damage to the eyes. In an ex vivo eye irritation study performed according to OECD TG 438, treatment of fresh enucleated chicken eyes with L-lactic acid produced corneal opacity, corneal swelling and fluorescein retention. The data are sufficient to warrant hazard classification for serious eye damage.

Based on the limited available data, the chemicals in this group are expected to be non-sensitising to the skin. In an in vivo skin sensitisation study, there was no significant difference in erythema between guinea pigs treated with L-lactic acid and controls. In a human repeat insult patch test, volunteers exposed to lactic acid (CAS No. 50-21-5) at concentrations of 2, 3, 4 or 5%, did not exhibit signs of sensitisation.

Due to the irritant properties of lactic acid, it is used under controlled conditions as a chemical skin peel. Available information on related alpha-hydroxy acids (AHAs) indicates that, for some time after application of these, the skin is sensitive to UV radiation.

Health hazard classification

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 does not consider classification of physical hazards and environmental hazards.

The proposed hazard classification is based on the read across principle (see **Grouping Rationale** section). It should be used as a default for all members of the group. If empirical

data become available for any member of the group indicating that a lower or higher classification is appropriate for the specific chemical, data may be used to amend the default classification for that chemical.

Health hazards	Hazard category	Hazard statement
Skin irritation	Skin Irrit. 2	H315: Causes skin irritation
Eye damage	Eye Damage 1	H318: Causes serious eye damage

Summary of health risk

Public

Australian and international data suggest widespread and repeated exposure of the public to some of the chemicals in this group through the use of rinse-off and leave-on cosmetic products, as well as domestic cleaning products. The main route of public exposure is expected to be dermal. Incidental inhalation, ingestion and contact with the eyes may also occur.

The US Food and Drug Administration (FDA) reviewed the safety of topically applied cosmetic products containing AHAs as ingredients. The evidence they reviewed suggests that AHAs increases the sensitivity of skin to the sun during use of the products, and up to a week after discontinuing use, and that this increased skin sensitivity to the sun may increase the possibility of sunburn. They recommended labelling for any cosmetic products, including those with exfoliant claims, containing AHAs with a warning about the risk of making the skin more sensitive to the sun and to use sunscreen for a week after discontinuing use of the product (US FDA 2005).

The US Cosmetic Ingredient Review (CIR) Expert Panel determined that lactic acid and other AHAs are safe in cosmetic products at concentrations up to 10% at a pH ≥3.5 with measures in place to avoid sun sensitivity, and at concentrations up to 30% at a pH ≥3.0 in salon products applied by trained professionals (CIR 1998; CIR 2017).

The chemicals in this group are not currently listed in the Poisons Standard (TGA 2021). Given the identified health hazards, the evidence indicates that there is a risk to the public that requires management (see **Recommendations** section).

Workers

Workers

During product formulation, dermal, ocular and inhalation 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.

Given the critical local health effects, these chemicals could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risk to workers (refer to **Recommendations** section).

Conclusions

The conclusions of this evaluation are based on the information described in this statement. Obligations to report additional information about hazards under Section 100 of the Industrial Chemicals Act 2019 apply.

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

Recommendations

Public health

Recommendation to Department of Health

It is recommended that the delegate of the Secretary for Poisons Scheduling includes lactic acid isomers 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, the entry should restrict the concentration and pH of the chemicals in cosmetic products.

Consideration should be given to the following:

- the use of the chemicals in multiple cosmetic products available in Australia, particularly in chemical skin peels or exfoliating products
- another AHA glycolic acid, which has similar physical properties and local irritation effects as lactic acid is listed in Schedule 6 when used in cosmetic products at a certain concentration and/or pH, based on it being also an irritant to the skin and eyes
- there is strong evidence showing that long term application of glycolic acid increases skin sensitivity to UV light. Based on the evidence from glycolic acid, it is expected that lactic acid present in cosmetic products, especially chemical peels, may increase skin sensitivity to UV light
- when used as an active ingredient in preparations for topical use, advisory statements are required for medicine labels
- the US FDA recommended labelling for any cosmetic product containing AHAs to warn against the risk of skin sensitivity to the sun
- the CIR review and conclusions on safety of AHAs in cosmetic products
- the restrictions in place in cosmetic products in other regions including Canada and Asia.

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.

Information on managing identified risks

The information in this report, 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 Model Work Health and Safety Regulations.

Recommended control measures that could be implemented to manage the risk arising from occupational exposure to the chemicals include, but are not limited to:

- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- regularly cleaning equipment and work areas
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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

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.

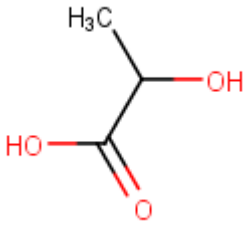
Model codes of practice, available from the SWA website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety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

Supporting information

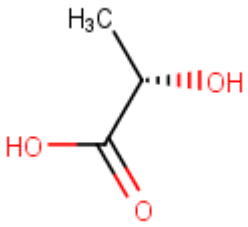
Grouping rationale

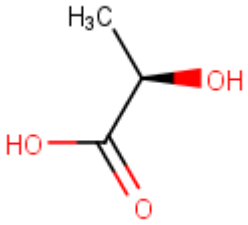
The 3 chemicals in this evaluation are isomers of lactic acid. DL-lactic acid (CAS No. 50-21-5) is the racemic mixture, L-lactic acid (CAS No. 79-33-4) is the levorotatory isomer, and D-lactic acid (CAS No. 10326-41-7) is the dextrorotatory isomer. Lactic acid isomers belong to the family of alpha-hydroxy acids (AHAs), which are carboxylic acids with one hydroxyl group attached to the alpha carbon. L-lactic acid is an endogenous mammalian metabolite involved in oxidation and gluconeogenesis. DL-lactic acid is present in many fermented milk products. Although most data are available for L-lactic acid, the chemicals in this group are assumed to have similar toxicological properties, based on their acidic properties.

Chemical identity

Chemical name	Propanoic acid, 2-hydroxy-
CAS	50-21-5
Synonyms	DL-lactic acid propanoic acid, 2-hydroxy-, (.±.)-
Structural formula	
Molecular formula	C3H6O3
Molecular weight (g/mol)	90.08
SMILES	CC(O)C(O)=O
Chemical description	racemic mixture

Chemical name	Propanoic acid, 2-hydroxy-, (S)-
CAS	79-33-4
Synonyms	L-lactic acid

Structural formula	
Molecular formula	C3H6O3
Molecular weight (g/mol)	90.08
SMILES	C[C@H](O)C(O)=O
Chemical description	levorotatory isomer

Chemical name	Propanoic acid, 2-hydroxy-, (2R)-
CAS	10326-41-7
Synonyms	D-lactic acid (2R)-2-hydroxypropanoic acid propanoic acid, 2-hydroxy-, (R)-
Structural formula	
Molecular formula	C3H6O3
Molecular weight (g/mol)	90.08
SMILES	C[C@@H](O)C(O)=O
Chemical description	dextrorotatory isomer

Relevant physical and chemical properties

Pure lactic acid is a crystalline substance that melts at room temperature. The chemical rapidly absorbs water and is normally produced as a highly concentrated solution. Lactic acid has a reported vapour pressure on 0.08 mm Hg (approx. 10 Pa) and a pKa of 3.85 (NCBI; REACH).

Introduction and use

Australia

Lactic acid is used in cosmetics in Australia. It is found in skin care products including exfoliators, cleansers, toners, creams, gels and peels, at concentrations up to 30%, based on an internet search. It is commonly present in combination with other AHAs, particularly glycolic acid.

Lactic acid has reported non-industrial uses:

- as an active, homoeopathic and excipient ingredient in therapeutic goods (TGA)
- as an active constituent in agricultural/veterinary chemical products (APVMA)
- in foods (FSANZ).

International

The following international uses have been identified through the:

- CIR database
- Consumer Product Information Database (CPID)
- European Chemicals Agency (ECHA)
- Environmental Working Group (EWG) Skin Deep database
- European Commission Cosmetic Ingredients and Substances (CosIng) database
- International Fragrance Association (IFRA) Transparency List
- Substances in Preparations in Nordic Countries (SPIN) database
- United States Personal Care Products Council.

Lactic acid and L-lactic acid have reported cosmetic uses, including in:

- skin care products (body wash, lotions, creams, cleansers, peels, exfoliators, serums, toners, face wipes) (up to 10%)
- nail care products (up to 10%)
- makeup and makeup removers (up to 8%)
- indoor tanning preparations (up to 6%)
- hair care products (conditioners, shampoos, colourants, treatments, detanglers, styling products) (up to 5%)
- bath oils, salts and soaks (up to 3%)
- deodorants (up to 1.7%)
- fragrances
- hand soaps and sanitisers
- oral hygiene products
- baby care products (shampoos, creams, lotions, soaps, wipes).

In cosmetic products, lactic acid functions as a:

- buffer
- humectant
- pH adjuster
- skin conditioning agent
- mild exfoliant.

Lactic acid and L-lactic acid have reported domestic uses, including in:

- laundry and dishwashing products (up to 18%)
- cleaning and furniture care products (up to 30%)
- adhesives and sealants
- air freshener products
- anti-freeze products
- arts, crafts and hobby materials
- automotive care products
- lubricants and greases
- paints and coatings.

Lactic acid and L-lactic acid have reported commercial uses in:

- the maintenance and repair of motor vehicles and motorcycles.

Lactic acid and L-lactic acid have reported site limited uses, including in the manufacture of:

- rubber, wooden and plastic products
- fabric, textile and leather products
- electronic products
- fabricated metal products
- vehicles and machinery
- chemicals and chemical products
- paper products (DL-lactic acid only)
- basic metals and other non-metallic mineral products (DL-lactic acid only).

D-lactic acid has reported site-limited uses, including in the manufacture of:

- chemicals
- plastic products.

Lactic acid and L-lactic acid have reported non-industrial uses in:

- agriculture
- pesticides
- pH regulators and water treatment products
- food flavourings.

Chemical peels

Lactic acid is used in superficial chemical peels at concentrations up to 30% (Soleymani et al. 2018). Superficial chemical peels penetrate the epidermis only, as opposed to medium and deep chemical peels which affect the papillary dermis and midreticular dermis, respectively. Superficial chemical peels containing lactic acid are used in the treatment of acne and pigmentation, and to improve the texture and appearance of facial skin (Rendon et al. 2010). They are usually applied to the skin by trained professionals (aestheticians) in salons for up to 10 minutes before being neutralised with dilute sodium bicarbonate solution (Soleymani et al. 2018). Superficial peels are usually well tolerated with mild discomfort (burning, irritation, erythema). The medical use of lactic acid is outside the scope of this evaluation.

AHAs, particularly when used at high concentrations, are known to act as exfoliants. A change in UV transmission, possibly due to the exfoliant activity of AHA applied on the skin could result in increased UV damage to epidermal cells (SCCNFP 2004). Therefore, warning statements on labels for cosmetic products with exfoliant claims are recommended by overseas regulatory authorities (refer to **International regulatory status** section).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for this group of chemicals.

Public

The chemicals in this group are not listed in the Poisons Standard (TGA 2021).

Lactic acid is listed in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019 (TGA 2019). When used as an active ingredient in preparations for topical use, the following advisory statements are required for medicine labels:

- This product may make your skin more sensitive to sunlight and other sources of UV light.
- Sun exposure should be limited by using a sunscreen and by wearing protective clothing.
- Transient stinging or irritation may occur when using this product. If irritation persists, discontinue use.
- If you have sensitive skin, test this product on a small area of skin before applying it to a large area.
- Not recommended for use on children and infants.

Workers

The chemicals in this group are not listed on the HCIS and no specific exposure standards are available (SWA).

International regulatory status

Exposure standards

The following temporary emergency exposure limits (TEELs) for lactic acid have been recommended by the United States Army Public Health Centre (USAPHC 2013):

- 500 mg/m^3 (TEEL-3)
- 100 mg/m^3 (TEEL-2)
- 15 mg/m^3 (TEEL-1).

Canada

Lactic acid and L-lactic acid are listed in the Cosmetic Ingredient Hotlist - List of Ingredients that are Restricted for Use in Cosmetic Products (Government of Canada 2019), under AHAs. The maximum permitted lactic acid concentration in skin products is:

- 10% at a pH ≥3.5 for consumer use
- 10–30% or a pH between 3.0–3.5 for professional use.

In addition, the following labelling is mandatory for all skin products containing AHAs at concentrations ≥3%:

- Use only as directed
- Avoid contact with the eyes
- If irritation persists, discontinue use and consult a physician
- It is recommended that prior to exposure to the sun, users cover areas where AHAs have been applied with sunscreen
- Contact of the product with the skin must be of limited frequency or duration.

AHAs (includes lactic acids) are included in the Human and Veterinary Prescription Drug List (requires a prescription) when used, alone or in combination with other ingredients, as part of an in-office chemical peel procedure.

European Union

The European Commission Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) reviewed the safety of lactic acid and other AHAs in cosmetic products (SCCNFP 2000). The SCCNFP considered a need for further studies evaluating the safety of the long term use of AHAs, as well as the effect of AHAs on skin responses to UV exposure and skin barrier function. Based on the precautionary principle, it was concluded that lactic acid is safe in cosmetic products at concentrations ≤2.5% at a pH ≥5. Recommendations on warnings to avoid contact with eyes and protect skin from UV exposure were also made.

In 2004, the SCCNFP reviewed its safety assessment of AHAs (SCCNFP 2004). New submitted data revealed that AHA application increases UV damage to the skin. The SCCNFP maintained its previous opinion due to inadequate data.

United States of America

The US FDA reviewed the safety of topically applied cosmetic products containing AHAs as ingredients. The evidence suggests that AHAs increases the sensitivity of skin to the sun during use of the products, and up to a week after discontinuing use, and that this increased skin sensitivity to the sun may increase the possibility of sunburn (US FDA 2005). The US FDA AHA Review Committee noted in the human clinical studies that investigated the effects of glycolic acid on UV sensitivity, a small proportion of people had increased sunburn cell (SBC) (apoptotic cells produced in response to UV radiation) formation or reduced minimal erythema dose (MED – the minimum amount of UV radiation needed to cause the skin to redden).

The US FDA (2005) recommended labelling for any cosmetic products containing AHAs intended for topical administration to the skin or mucous membranes that are exposed to the sun. The following warning statement is recommended: “Sunburn Alert: This product

contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear protective clothing, and limit sun exposure while using this product and for a week afterwards". A similar warning statement is also recommended for cosmetic products with exfoliant claims.

The CIR Expert Panel conducted a safety assessment of lactic acid and other AHAs (CIR 1998). It was concluded that lactic acid is safe in cosmetic products at concentrations of:

- ≤10% at a pH ≥3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection
- ≤30% at a pH ≥3.0 in salon products designed for brief discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals and when application is accompanied by directions for the daily use of sun protection.

In 2017, the CIR Expert Panel reviewed its safety assessment of AHAs and confirmed its original conclusion (CIR 2017).

Asia

Lactic acid is listed in the ASEAN Cosmetic Directive Annex III - List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down (HSA 2020). The maximum authorised lactic acid concentration in ready to use skin products is:

- ≤10% at a pH ≥3.5 for general use
- >10–20% at a pH ≥3.0 for professional use
- >20% at a pH ≥3.0 for use by a qualified medical practitioner.

In addition, the following labelling is mandatory for skin products containing lactic acid at concentrations ≥2.5% that do not contain a sunscreen and are intended to be applied to sun exposed areas of the body:

- Sunburn alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear sun protective clothing, and limit sun exposure while using this product and for a week afterwards.

Health hazard information

Toxicokinetics

The dermal absorption of L-lactic acid was investigated in an in vitro study using flow-through diffusion cells. Porcine dorsal skin discs (7 females/dose) were exposed to the chemical (8%) through oil-in-water (o/w) emulsions for 6 hours under acidic (pH 3.8; lactic acid is 50% ionised) and basic (pH 7.0; >99.9% ionised) conditions. The chemical was applied as either a 2 µL topical non-occluded film (finite dose: examining the hydrophobic pathway) or a 75 µL occluded patch (infinite dose: examining the hydrophilic pathway). When applied as a finite dose, 25% and 6.5% of the initial dose penetrated the skin, at pH 3.8 and pH 7.0, respectively. When applied as an infinite dose, 0.5–0.9% of the initial dose penetrated the skin at both pH conditions. The transdermal permeability coefficient for lactic acid was significantly higher in the infinite dose application. For both application modes, propylene glycol (5%) significantly enhanced L-lactic acid delivery to the epidermis. Water-in-oil (w/o)

and water-in-oil-in-water (w/o/w) emulsions delivered less lactic acid to the skin compared to o/w emulsions (Sah et al. 1998).

When applied to the skin, AHAs cause accelerated cell turnover in the stratum corneum, by reducing intercorneocyte cohesion and interfering with intercellular ionic bonding. Maximum cell turnover is observed at a pH 3, while products containing AHAs stimulate the highest rate of cell turnover at a pH ranging from 2.8–4.8 (SCCNFP 2004). This exfoliant activity may lead to increased UV damage to the epidermal cells of the skin.

Acute toxicity

Oral

Based on the available data, the chemicals in this group are expected to have low acute oral toxicity. The data do not warrant hazard classification.

In a good laboratory practice (GLP) compliant in vivo acute oral toxicity study conducted similarly to OECD TG 401, albino rats (5/sex/dose; strain unspecified) were treated with a single dose of L-lactic acid by oral gavage at dose levels of 4467, 5012, 5623 or 6310 mg/kg bw (without negative control animals). Female rats (5/dose) were also administered the test chemical at dose levels of 3162, 3548 or 3981 mg/kg bw. The LD50 for acute oral toxicity was determined to be 3543 mg/kg bw for females and 4936 mg/kg bw for males. Male mortality rates during the 14 day observation period for the dose groups 4467, 5012, 5623 and 6310 mg/kg bw were 20%, 60%, 80% and 100%, respectively. Female mortality rates during the observation period for the dose groups 3162, 3548, 3981, 4467, 5012, 5623 and 6310 mg/kg bw were 20%, 40%, 100%, 100%, 100%, 100% and 100%, respectively. Reported sublethal signs of toxicity included lethargy, ataxia (lack of coordination), prostration, irregular breathing, piloerection, squinting, lacrimation, salivation, crusty eyes and muzzle, loose stools, damp or yellow/brown stained fur and moribundity (lack of vitality). Observations at necropsy included: discolouration of the lungs, stomach, liver, diaphragm and kidneys; stomach erosion, distension, ulceration, haemorrhage and mucosal sloughing; foci in the lungs and liver; mottled lungs and liver; pale capsular areas and superficial erosion of the liver; and red-brown exudate in the nasal and/or oral regions (OECD 2010; REACH).

In other acute oral toxicity studies, the LD50 for DL-lactic acid was determined to be 1810 mg/kg bw in guinea pigs, 4875 mg/kg bw in mice and >2250 mg/kg bw in quail. Sublethal signs of toxicity were not reported (CCOHS 2021).

No data are available for the other chemicals in this group.

Dermal

Based on the available data, the chemicals in this group are expected to have low acute dermal toxicity. The data do not warrant hazard classification.

In a GLP compliant in vivo acute dermal toxicity study conducted similarly to OECD TG 402, New Zealand White (NZW) rabbits (5/sex) were treated with a single dose of L-lactic acid at 2000 mg/kg bw on abraded skin for 24 hours under occlusive conditions. The LD50 for acute dermal toxicity was determined to be >2000 mg/kg bw for both sexes. No mortalities occurred during the 14 day observation period. Severe erythema and oedema were observed at the test sites of all animals on day 1, but both decreased in severity by day 14. Other reported dermal reactions included blanching, necrosis (brown-green discolouration), eschar, desquamation (skin peeling), fissures and denuded areas along abrasion lines.

Atonia (loss of muscle strength) was observed in the animals. Observations at necropsy included skin depressions and discolouration, and dark red foci in the lungs (OECD 2010; REACH).

No data are available for the other chemicals in this group.

Inhalation

Based on the available data, the chemicals in this group are expected to have low acute inhalation toxicity. The data do not warrant hazard classification.

In a GLP compliant in vivo acute inhalation toxicity study conducted similarly to OECD TG 403, Fischer 344 (F344) rats (5/sex/dose) were exposed to L-lactic acid as an aerosol through the nose only for 4 hours at a concentration of 0 or 7.94 mg/L. The mass median aerodynamic diameter ranged from 2.03–2.15 µm, with a mean of 2.09 µm. The LC50 for acute inhalation toxicity was determined to be >7.94 mg/L. The mortality rate during the 14 day observation period was 10%. Reported sublethal signs of toxicity included rapid breathing, eye tearing, hunched posture, ruffled and stained coats (OECD 2010; REACH).

No data are available for the other chemicals in this group.

Corrosion/Irritation

Skin irritation

Based on the available data, the chemicals in this group are expected to be skin irritants. The data are sufficient to warrant hazard classification as skin irritants.

In a GLP compliant in vivo skin irritation study conducted in accordance with OECD TG 404, New Zealand White rabbits (6/group) were topically treated with L-lactic acid (88% aqueous solution) on either intact or abraded skin for 4 hours under semi-occlusive conditions. Observations were recorded at 0, 24, 48 and 72 hours, and 7 and 21 days after patch removal. The following mean scores were reported in the intact skin group at 0, 24, 48 and 72 hours: 5.8, 5.5, 3.8 and 3.7, respectively for overall irritation (maximum score of 8); 3.7, 3.7, 3.7 and 3.7, respectively for erythema (maximum score of 4); and 2.2, 1.8, 0.2 and 0, respectively for oedema (maximum score of 4). The following mean scores were reported in the abraded skin group at 0, 24, 48 and 72 hours: 6.2, 6.0, 4.0 and 4.0, respectively for overall irritation (maximum score of 8). Very slight to slight ischemic necrosis, moderate to severe haemorrhage and slight to moderate oedema were observed at 0 and 24 hours, and were fully reversible within 2 days. Other signs of skin irritation included moderate to severe encrustations, formation of scar tissue and absence of hair growth. The chemical was considered to be severely irritating and corrosive to rabbit skin under the conditions of this study (OECD 2010; REACH).

In a GLP compliant in vivo skin irritation study conducted similarly to OECD TG 404, guinea pigs (strain and sex unspecified) (3/group) were topically treated with L-lactic acid (88% aqueous solution) for either 1 or 4 hours under semi-occlusive conditions. Observations were recorded 1, 24, 48 and 72 hours after patch removal. No irritation was observed in the 1 hour exposure group. Very slight erythema was observed in the 4 hour exposure group within 1 hour of patch removal. This was fully reversible within 24 hours. The chemical was considered to be slightly irritating to guinea pig skin under the conditions of this study (OECD 2010; REACH).

In a GLP compliant in vivo skin irritation study conducted similarly to OECD TG 404, pigs (large white crossed with Dutch landrace) (3 males) were topically treated with L-lactic acid (88%) for 3 minutes, 1 hour and 4 hours under occlusive conditions. Observations were recorded 1, 24, 48 and 72 hours, and 7, 14 and 21 days after patch removal. No skin irritation was observed. The chemical was not considered to be irritating to pig skin under the conditions of this study (OECD 2010; REACH).

In a GLP compliant in vitro skin irritation study, isolated skin discs were obtained from one NZW rabbit (male) and one human (female) and exposed to L-lactic acid (88% aqueous solution) for 30 minutes. Treated skin discs were compared to untreated controls. Toxicity was determined by examining tetrazolium salt conversion. Rabbit skin was found to be more sensitive to lactic acid compared to human skin (REACH).

No data are available for the other chemicals in this group.

Eye irritation

Based on the available data, the chemicals in this group are expected to cause serious damage to the eyes. The data is sufficient to warrant hazard classification as serious eye damage.

In a GLP compliant ex vivo eye damage/irritation study conducted similarly to OECD TG 438, 3 fresh enucleated chicken eyes were exposed to L-lactic acid (88%; 0.03 mL aqueous solution or 0.03 g solid) for 10 seconds before being rinsed with 20 mL saline solution. The control eye and test eyes were examined pre-treatment, and at 0, 30, 75, 120, 180 and 240 minutes after the post treatment rinse. All 3 eyes exhibited corneal opacity, corneal swelling and fluorescein retention. The mean corneal opacity score was 4/4 at 240 minutes. The mean corneal swelling score was 28.3% at 240 minutes. The mean fluorescein retention score was 3/3 at 30 minutes. The chemical was considered to cause serious damage to chicken eyes under the conditions of this study (REACH).

No data are available for the other chemicals in this group.

Sensitisation

Skin sensitisation

Based on the available data, the chemicals in this group are expected to be non-sensitising to the skin.

In a GLP compliant in vivo skin sensitisation study, Hartley guinea pigs (10 females/group) were treated with L-lactic acid in deionised water under occlusive conditions for 6 hours. During the induction phase, the chemical was applied 3 times per week for a total of 9 applications. The first 2 induction applications of the chemical were at 100%, and the remaining applications were reduced to 30%. After 14 days, the animals received a single challenge application of the chemical at 100%. A naïve control group was treated with the chemical at challenge only, without receiving any induction applications. Observations were recorded 24 and 48 hours after each treatment. Severe erythema (grade 4) was noted for 6/10 treated animals and 8/10 naïve control animals. These skin reactions were considered to result from irritation rather than sensitisation. The chemical was considered to be non-sensitising to guinea pig skin under the conditions of this study (OECD 2010; REACH).

No data are available for the other chemicals in this group.

Observations in humans

In a human repeat insult patch test, lactic acid (2, 3, 4 or 5%) was applied topically to the skin of 99 volunteers under semi-occlusive conditions for 24 hours, 3 times per week for a total of 10 exposures. After 14 days, an open patch challenge application was made to the original site and to a previously untreated site. Observations were recorded 24 and 48 hours after treatment. After 48 hours, mild erythema was observed in one volunteer exposed to 2% lactic acid, and another volunteer exposed to 3% lactic acid. No clinically significant responses were observed in these 2 volunteers upon rechallenge. The chemical was considered to be non-sensitising to human skin under the conditions of this study (REACH).

No data are available for the other chemicals in this group.

Repeat dose toxicity

Oral

No data are available for the chemicals in this group. Calcium lactate pentahydrate (CAS No. 5743-47-5) is the calcium salt of lactic acid (isomer not specified) and has been used in one repeat dose toxicity study as a supporting chemical. Based on the read-across information from the analogue, the chemicals in this group are not expected to cause serious overt systemic health effects following repeated oral exposure.

In a non-GLP compliant in vivo repeat dose toxicity study conducted similarly to OECD TG 408, calcium lactate pentahydrate was orally administered to F344 rats in 2 separate experiments. Experiment I: F344 rats (5/sex/dose) were administered calcium lactate pentahydrate in drinking water at 0, 0.3, 0.6, 1.25, 2.5 or 5% (equivalent to 0, 30, 60, 125, 250 or 500 mg/kg bw/day) for 90 days. No mortalities occurred. Reported effects, which were not considered to be adverse, included decreased body weight gain in the 500 mg/kg bw/day dose group, and some haematological and biochemical changes (not specified). No significant toxicological findings were reported. The reported NOAEL for calcium lactate was determined to be 500 mg/kg bw/day. Experiment II: F344 rats (10/sex/dose) were administered calcium lactate pentahydrate in feed at 0, 5, 10, 20 or 30% for 20 weeks. Reported effects included decreased body weight gain in the 30% dose group. Nephrocalcinosis (calcium deposits in the kidneys) was observed in all dose groups including controls; however a follow-up study concluded that it was related to the high calcium/phosphate (Ca/P) ratio of the diet, and not to lactate toxicity (OECD 2010; REACH).

Dermal

Based on the available data, the chemicals in this group are not expected to cause serious overt systemic health effects following repeated dermal exposure.

In a non-GLP compliant in vivo repeat dose toxicity study, Sprague Dawley rats (15 females/group) were administered lactic acid by topical dermal application at 0 or 0.25% (equivalent to 886 mg/kg bw/day), 5 times per week for 13 weeks. No mortalities occurred. Reported adverse effects included minimal skin irritation, significantly increased blood urea nitrogen values, increased absolute brain weight, and increased kidney-to-body weight ratios. The reported LOAEL for lactic acid was determined to be 886 mg/kg bw/day for female rats (REACH).

No data are available for the other chemicals in this group.

Genotoxicity

Based on the available data, the chemicals in this group are not expected to have genotoxic potential.

Negative results were reported in the following in vitro genotoxicity studies:

- In a non-GLP compliant bacterial reverse mutation assay conducted similarly to OECD TG 471, *Salmonella typhimurium* strains TA92, TA94, TA98, TA100, TA1535, TA1537 and TA2637 were treated with L-lactic acid. Negative results were reported with and without metabolic activation at concentrations up to 10 mg/plate (OECD 2010; REACH).
- In a non-GLP compliant bacterial reverse mutation assay conducted similarly to OECD TG 471, *Escherichia coli* strains B/Sd-4/1,3,4,5 and B/Sd-4/3,4 were treated with lactic acid. Negative results were reported without metabolic activation at concentrations up to 0.02% (REACH).
- In a non-GLP compliant bacterial reverse mutation assay conducted similarly to OECD TG 471, *S. typhimurium* strains TA97, TA98, TA100 and TA104 were treated with lactic acid. Negative results were reported with and without metabolic activation at concentrations up to 2.0 µL/plate (CIR 1998; REACH).
- In a non-GLP compliant in vitro mammalian chromosome aberration test conducted similarly to OECD TG 473, Chinese hamster ovary (CHO) cells were treated with L-lactic acid at doses of 10–16 and 8–14 mM. Negative results were reported with and without metabolic activation when the medium was neutralised to physiological pH 6.4. Limited details are available for this study (CIR 1998; OECD 2010; REACH).
- In a non-GLP compliant in vitro mammalian chromosome aberration test conducted similarly to OECD TG 473, Chinese hamster lung fibroblasts (V79) were treated with lactic acid. Negative results were reported with and without metabolic activation at concentrations of 10 mg/plate (REACH).

No data are available for the other chemicals in this group.

Carcinogenicity

Limited data are available for the chemicals in this group. Calcium lactate pentahydrate has been used in one carcinogenicity study as a supporting chemical. Based on the limited data and read-across information from the analogue, the chemicals in this group are not expected to be carcinogenic following long-term oral exposure.

In a non-GLP compliant in vivo carcinogenicity study, lactic acid was orally administered to rabbits in 2 separate experiments. Experiment I: rabbits (female, number not specified) were administered lactic acid in drinking water at dose levels of 0.1–0.2 g/kg bw, twice daily for 5 months. Experiment II: rabbits (5 females) were administered lactic acid in drinking water at dose levels of 0.1–0.7 g/kg bw, twice daily for 16 months. No tumours were reported. The chemical was considered to be non-carcinogenic under the conditions of this study (CIR 1998; REACH).

In a non-GLP compliant in vivo combined chronic toxicity and carcinogenicity study conducted similarly to OECD TG 453, F344 rats (50/sex/dose) were administered calcium lactate pentahydrate in drinking water at 0, 2.5 or 5% for 2 years. Reported effects included decreased body weight gain, with a 13% decrease in the highest dose group. Kidney weights of females in the highest dose group were significantly higher compared with the controls; however, no histological change in the severity of chronic nephropathy was observed between the dose groups. Tumours were found in many organs and tissues in all dose

groups including control animals; however, the tumours observed in this experiment were similar to those known to occur spontaneously in F344 rats. None of the treatment dose groups showed a significant increase in the incidence of any specific tumours compared with the controls. The no observed adverse effect concentration (NOAEC) for calcium lactate was 5% for both sexes. The chemical was considered to be non-carcinogenic under the conditions of this study (CIR 1998; OECD 2010; REACH).

Reproductive and development toxicity

Based on the available data, the chemicals in this group are not expected to cause specific adverse effects on development following oral exposure.

In a non-GLP compliant in vivo developmental toxicity study, pregnant Swiss albino CD-1 mice (12/dose) were administered lactic acid by gavage at dose levels of 0 or 570 mg/kg bw/day on gestational days (GD) 6–15. The animals were sacrificed on GD 18. Reported maternal signs of toxicity included decreased liver weight and decreased feed consumption. Reported foetal signs of toxicity included delayed ossification of parietal bones which was attributed to decreased foetal weight. The NOAEL for maternal and foetal toxicity was determined to be 570 mg/kg bw/day (CIR 1998; OECD 2010; REACH).

No data are available for the other chemicals in this group.

Phototoxicity

Based on the available data, the chemicals in this group are expected to be weak phototoxins.

In 2 in vivo phototoxicity studies consisting of 7 separate experiments, a face cream containing 0.25% of 85% lactic acid was applied to the skin of NZW rabbits (6/experiment) for 15–30 minutes before exposure to a UV light source for 1–2 hours. 8-Methoxypsoralen was used as a positive control. Test sites were scored using the Draize scale for erythema and oedema at 24, 48, 72 and 96 hours after application. The face cream containing the chemical was considered to be a weak phototoxin under the conditions of these studies (CIR 1998).

Sensitivity to UV light

The available data examining the effects of lactic acid on skin sensitivity to UV light are inconclusive. Studies in humans using glycolic acid (CAS No. 79-14-1), which has similar structural and physical properties (molecular weight) and local irritation effects, have shown that it increases the risk of skin sensitivity to UV light. Based on the available read across data, the ability of the chemicals to increase the sensitivity of skin to UV light cannot be ruled out.

The MED is the amount of UV radiation that will produce minimal erythema, and is a marker of lethal DNA damage induced by UV radiation. In a study examining the effect of AHAs on skin sensitivity to UV, 14 human subjects were topically treated on the mid back region of each subject with either 10% glycolic acid (pH 3.5), vehicle or no treatment, once daily, 5 days per week for 3.5 weeks. After the last treatment, the test sites were exposed to UVB radiation equivalent to 1–1.6 MED (determined for each subject), and biopsy samples were obtained. A significant increase in the number of SBCs, erythema intensity and lower MED, were observed at test sites treated with glycolic acid compared with vehicle treated or untreated sites. Treatment with glycolic acid resulted in a significantly increased cyclobutane

pyrimidine dimers (CPD; marker of DNA damage). Glycolic acid was considered to increase the sensitivity of human skin to UV under the conditions of this study (Kornhauser et al. 2009).

In a double blind randomised study examining the effect of glycolic acid on skin sensitivity to UV, 29 human subjects were topically treated with 10% glycolic acid (pH 3.5) or placebo (similar composition (pH 3.5) without glycolic acid), once daily, 6 days per week for 4 weeks. After the last treatment, one group of subjects (n = 16) was exposed to UV light to determine the MED and induce SBC formation, while the other group (n = 13) was exposed to UV light equivalent to 1.5 MED (individually determined) to induce CPD formation. Biopsy samples were obtained from irradiated sites. A significantly increased average number of SBCs and decreased MED values (-18%) were observed at test sites treated with glycolic acid compared with the placebo or untreated sites. The average number of CPD was increased, but was not statistically significant. After a week of discontinuing treatment, the number of SBCs and MED values were no longer significantly different from placebo or untreated sites, which suggest that the increased UV sensitivity was reversible one week after discontinuing glycolic acid application (Kaidbey et al. 2003).

In a vehicle controlled study examining SBC production, 3 groups of 15–16 human subjects were topically treated with 10% glycolic acid gel (pH 3.5–4.0), once daily for 4 days or 12 weeks. After the last treatment, the test sites were exposed to UV light equivalent to 1.0 MED (individually determined), and biopsy samples were obtained from each site after 16–24 hours of irradiation. The number of sunburn cells were examined microscopically. No effects were observed at test sites treated with glycolic acid for 4 days. Significantly increased SBC production was observed at test sites treated with glycolic acid for 12 weeks compared with untreated control sites, or vehicle control treated sites. Long term treatment with glycolic acid (10%) increases skin sensitivity to UV radiation under the conditions of this study (CIR 1998; NICNAS 2000).

In a double blind, vehicle controlled randomised study examining SBC production, 9 human subjects with mild to moderate photodamaged skin were topically treated with 8% lactic acid (pH 3.89) or vehicle (pH 7.55) (1 g) twice daily for 22 weeks and instructed to wear sunscreen. After treatment, 18 paired skin biopsy samples were obtained from the forearms. A total of 4 SBCs (180 fields examined) were identified in the treated skin biopsy samples. No SBCs were observed in the vehicle treated samples. The increase in SBC production was not significant (CIR 1998).

In a double blind, vehicle controlled randomised study examining SBC production, 12 human subjects were topically treated with 8% lactic acid (pH 3.89) and 8% glycolic acid (pH 3.8) or vehicle (pH 7.55) (1 g) twice daily for 22 weeks and instructed to wear sunscreen. After treatment, 24 paired skin biopsy samples were obtained. A total of 3 SBCs (240 fields examined) were identified in the treated samples. No SBCs were observed in the vehicle treated samples. The increase in SBC production was not significant (CIR 1998).

In a study examining the effect of AHAs on the MED, the ventral forearms of 20 human subjects were topically treated with a formulation containing lactic acid and 2 other AHAs (alpha hydroxyl octanoic acid and alpha hydroxyl decanoic acid) at a concentration of 1.4%. The formulation was applied to one ventral forearm of each subject, twice a day for 3 months. UVB exposure to both forearms occurred at 4, 8 and 12 weeks to determine if there is a change in the MED. In addition, the subjects were exposed to 1.5 times their MED at study initiation and 4, 8 and 12 weeks after application of the formulation. Erythema was assessed 24 hours after UV exposure. No changes in the MED were observed 24 hours after application or in the skin reactivity after exposure to 1.5 times their MED compared to the untreated site. No significant changes in skin responses to UV were observed after 3 months of treatment with AHAs (CIR 1998).

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