Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Maleic acid salts

Evaluation statement

14 January 2022

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AICIS Evaluation Statement

Subject of the Evaluation

Maleic acid salts

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2-Butenedioic acid, (Z)-, potassium salt	10237-70-4
2-Butenedioic acid, (Z)-, sodium salt	18016-19-8
2-Butenedioic acid, (Z)-, diammonium salt	23705-99-9

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 this chemical group of salts of maleic acid. These chemicals have been assessed as a group as they have a common ionic component (maleate) and are expected to have similar bioavailability.

Summary of Evaluation

Summary of Introduction, Use and End Use

There is currently no specific information about the introduction, use and end use of this group of chemicals in Australia.

Most of the information on uses of the chemicals comes from the SPIN (Substances in Preparation in Nordic Countries) database. While the SPIN database indicates domestic uses, the database does not distinguish between direct use of the chemical or use of the materials that are produced from chemical reactions involving the chemical.

Sodium and disodium maleate (CAS Nos. 18016-19-8 and 371-47-1) have reported use in domestic products overseas (Chemwatch; DeLima Associates; SPIN).

Sodium maleate is present in household products, including air fresheners for homes and cars (DeLima Associates). Disodium maleate have reported use in household cleaning products as well as commercial and industrial settings (SPIN).

No information on concentration of the chemicals in domestic products is available.

Diammonium maleate (CAS 23705-99-9) has reported use in photochemicals (SPIN). Potassium maleate (CAS 10237-70-4) has reported non-industrial use in pesticides (SPIN).

Some therapeutic agents are manufactured as maleate salts (FDA 2011; Gupta et al. 2018; Shikino et al. 2017; TGA 2021; Ueno T et al. 2007).

Human Health

Summary of health hazards

The critical health effects for risk characterisation are derived from maleic acid:

- systemic acute effects from oral exposure
- local effects (skin sensitisation)
- systemic effects following repeated oral exposure.

Maleic acid salt toxicity is driven by the free maleate ion with speciation being dependent on pH, buffering capacity and ionic composition of the vehicle. Systemic effects are expected to reflect maleic acid toxicity (AICIS 2021a). Therefore, this evaluation is focusing on the potential difference in local effects produced by the salts, compared with maleic acid. There is uncertainty about the potency of local effects given the theoretical differences in dermal absorption for the salts compared to maleic acid.

Absorption by the dermal route is expected to be lower than that of maleic acid and be dependent on the vehicle. The pKa of maleic acid is very low. Therefore, at any physiological pH, maleate will be the predominant species with some monohydrogen maleate also being present. Ionised species usually have lower dermal absorption compared with neutral forms of the same chemical (WHO 2006). Therefore, at physiological pH when the maleate ion is the predominant species, dermal absorption is predicted to be lower than for maleic acid.

Maleic acid salts may have skin and eye irritation properties, although to a lesser extent than maleic acid. Disodium maleate was reported to have mild effects on the eyes of rabbits in a Draize test with no further details reported (CCOHS 2021). No data are available for the other salts. In the absence of more information, the salts are not recommended for classification as skin and eye irritants.

No skin sensitisation data are available for maleic acid salts; however allergic reactions to pharmaceutical formulation containing maleate has been reported. Based on data for other maleic acid derivatives (AICIS 2021a; AICIS 2021b), maleic acid salts have skin sensitisation potency. The sensitisation potency is likely dependent on dermal absorption. Therefore, the maleic acid salts are expected to be less potent sensitisers compared to maleic acid and maleic acid esters (AICIS 2021a; AICIS 2021b).

Allergic reactions to maleate based compound drugs have been reported (FDA 2011; TGA 2021). Allergic reactions were reported with the use of the sublingual drug asenapine maleate. Of the 52 cases, 15 reported a resolution of symptoms following drug discontinuation, while two of these cases reported a reappearance of symptoms upon

reintroduction of the drug. It is unknown whether the allergic reactions were caused by the active drug asenapine or to the maleate counter ion (FDA 2011). The TGA database of adverse event notifications (DAEN) contains reports of lip swelling, burning mouth, tongue erythema, tongue discomfort and general oral discomfort in patients taking sublingual asenapine maleate (TGA 2021). Case studies of allergic reactions to chlorphenamine maleate are available. However, it is unknown whether the allergic reactions are caused by the chlorphenamine or the maleate counter ion (Shikino et al. 2017; TGA 2021; Ueno et al. 2007).

Health Hazard Classification

Based on the available data for maleic acid, these chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Some of these recommended classifications are based on read across principles (see **Supporting Information - Rationale section**). If empirical data become available for any member of the group indicating that a lower (or higher) classification is appropriate for a specific chemical, this data may be used to amend the default classification for that chemical.

Health Hazards	Hazard Category	Hazard Statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Skin sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction

Summary of Health Risk

Public

Based on the available use information, the public may be exposed to the sodium or disodium maleate:

- by incidental skin and eye contact with the chemicals during use of domestic products
- by inhaling aerosols.

Evidence of domestic use of the chemicals is limited. No cosmetic use was identified.

Based on the limited information on domestic use and the fact that maleic acid is mainly used as a pH adjuster, frequent exposure to the chemicals at high concentrations is unlikely. Sensitisation, irritation and systemic effects are not expected to be a concern.

Therefore, there are no identified risks to the public that require management.

Worker

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 the chemicals at lower concentrations could 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. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical systemic long term, systemic acute and local health effects, the 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 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

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 hazard classifications, should be used by persons conducting a business or undertaking at the workplace (such as an employer) to determine the appropriate controls under the Model Work Health and Safety Regulations.

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

- 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
- 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 the chemical.

Measures required to eliminate, or manage risks arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, 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. 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 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.

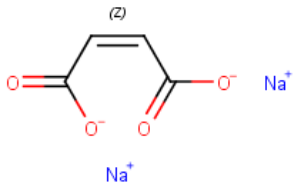
Supporting Information

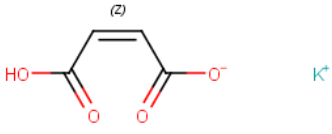
Grouping Rationale

The chemicals in this group are simple salts of maleic acid (CAS No. 110-16-7).

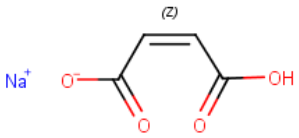
The chemicals in this evaluation are salts (sodium, potassium and ammonium) of maleic acid listed on the Inventory. The evaluation for maleic acid (AICIS 2021a) should be read in conjunction with this evaluation.

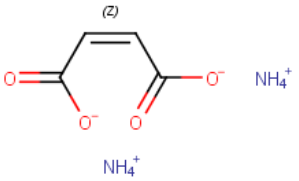
Chemical Identity

Chemical name	2-Butenedioic acid, (Z)-, disodium salt
CAS	371-47-1
Synonyms	disodium maleate
	maleic acid, disodium salt
Structural Formula	
Molecular Formula	C4H4O4.2Na
Molecular Weight (g/mol)	160.036
SMILES	[Na+].[Na+].[O-]C(=O)\C=C/C(=O)[O-]
Chemical Description	-

Chemical name	2-Butenedioic acid, (Z)-, potassium salt
CAS	10237-70-4
Synonyms	maleic acid, potassium salt
	potassium maleate
Structural Formula	

Molecular Formula	C4H4O4.xK
Molecular Weight (g/mol)	192.25
SMILES	[K+].OC(=O)\C=C/C([O-])=O
Chemical Description	-

Chemical name	2-Butenedioic acid, (Z)-, sodium salt
CAS	18016-19-8
Synonyms	maleic acid, sodium salt
	sodium maleate
Structural Formula	
Molecular Formula	C4H4O4.xNa
Molecular Weight (g/mol)	138.05
SMILES	[Na+].OC(=O)\C=C/C([O-])=O
Chemical Description	-

Chemical name	2-Butenedioic acid, (Z)-, diammonium salt
CAS	23705-99-9
Synonyms	maleic acid, diammonium salt
	diammonium maleate
Structural Formula	
Molecular Formula	C4H4O4.2H3N
Molecular Weight (g/mol)	150.133

SMILES	[NH4+].[NH4+].[O-]C(=O)\C=C/C([O-])=O
Chemical Description	-

Relevant Physical and Chemical Properties

The chemicals in this group have low molecular weights ranging between 138–200 g/mol. They are highly hydrophilic. Maleic acid has a first pKa of 1.9 and a second pKa of 6.2 (AICIS, 2021a). They are salts of acid base reactions between maleic acid and moderate to strong inorganic bases, including potassium hydroxide KOH, sodium hydroxide NaOH and ammonia NH_3 (Chemwatch; NCBI; NLM).

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

The chemicals are not listed as hazardous chemicals on the Hazardous Chemicals Information system (HCIS) and no exposure standards are available for the chemicals in Australia (SWA).

International regulatory status

Exposure standards

The following Temporary Emergency Exposure Limits (TEELs) are available for disodium maleate (Chemwatch; US Department of Energy, 2018):

- TEEL-1 = 13 mg/m^3, concentration of the chemical ‘above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, these effects are not disabling, are transient and reversible upon cessation of exposure.’ (US DOE 2018)
- TEEL-2 = 150 mg/m^3, concentration of the chemical ‘above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience irreversible or other serious, long-lasting, adverse health effects or an impaired ability to escape.’ (US DOE 2018)
- TEEL-3 = 880 mg/m^3, concentration of the chemical ‘above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience life-threatening adverse health effects or death.’ (US DOE 2018)

As stated by the US DOE, TEELs are intended for use until AEGLs (Acute Exposure Guideline Levels) or ERPGs (Emergency Response Planning Guidelines) are adopted for chemicals.

No exposure standards are available for the other salts.

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