Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Maleic acid esters (medium to long Chain)

Evaluation statement

14 January 2022

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

Maleic acid esters (medium to long chain)

Chemicals in this evaluation

Name	CAS Registry Number
2-Butenedioic acid, (Z)-, bis(2-ethylhexyl) ester	142-16-5
2-Butenedioic acid, (Z)-, dicyclohexyl ester	621-13-6
2-Butenedioic acid, (Z)-, diisooctyl ester	1330-76-3
2-Butenedioic acid, (Z)-, monooctyl ester	2370-71-0
2-Butenedioic acid, (Z)-, monooctadecyl ester	2424-62-6
2-Butenedioic acid, (Z)-, didodecyl ester	2915-52-8
2-Butenedioic acid, (Z)-, dioctyl ester	2915-53-9
2-Butenedioic acid, (Z)-, mono(2-ethylhexyl) ester	7423-42-9
2-Butenedioic acid, (Z)-, monohexyl ester	15420-81-2
2-Butenedioic acid, (Z)-, monoisooctyl ester	30137-97-4
2-Butenedioic acid, (Z)-, diisotridecyl ester	53817-59-7
2-Butenedioic acid, (Z)-, isodecyl ester	68186-70-9
2-Butenedioic acid, (Z)-, mono-C12-15-alkyl esters	68584-36-1
2-Butenedioic acid, (Z)-, mono-C16-18-alkyl esters	68987-59-7
2-Butenedioic acid, (Z)-, di-C8-10-alkyl esters	85566-60-5

Reason for the evaluation

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

Parameters of evaluation

These 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 group of chemicals of structurally similar maleate esters. These chemicals have been

assessed as a group as they have a common metabolite (maleic acid) and are expected to have similar toxicity and 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.

No international use data have been identified for the monoesters of this group of chemicals, except for mono(2-ethylhexyl) maleate (CAS No. 7423-42-9) which is used in commercial products (in lubricants and additives), and as an intermediate in chemical manufacturing. The diesters are used internationally in a range of industrial applications, including in cosmetic and personal care products (perfumes, skin conditioning) and domestic products (paints and varnishes). Diesters have various commercial uses, including as intermediates in chemical manufacturing.

Human health

Summary of health hazards

The critical health effects for risk characterisation include:

- systemic acute effects from oral exposure (mono(2-ethylhexyl) maleate)
- local effects [skin sensitisation (all chemicals), and corrosivity (monoesters only)].

In addition, the chemicals have moderate acute toxicity, and, at higher exposures, mono(2-ethylhexyl) maleate and diethylhexyl maleate, may be harmful for foetal development.

The limited available information on maleic esters and structurally similar chemicals suggest that these chemicals are readily absorbed via the oral and dermal routes. Maleic esters hydrolyse to maleic acid under aqueous conditions. Therefore, maleic acid is expected to be the main form available systemically, following oral uptake.
The limited available data for the diesters suggest that these chemicals have low acute toxicity vial the oral and dermal routes. The monoesters are expected to have low acute toxicity except for mono(2-ethylhexyl) maleate that has moderate acute toxicity via the oral route.

The long chain diesters in this group are not expected to be irritating to skin or eyes. Based on the data for mono(2-ethylhexyl) maleate, short chain monoesters and physico-chemical properties, the long chain monoesters in this group are expected to be corrosive to skin and cause serious eye damage.

The maleic diesters are considered to be skin sensitisers based on animal data reported in studies. This is supported by observations in humans where sensitisation reactions were reported in human patch test studies at concentrations 5–10%. The monoesters are considered to be skin sensitisers based on the data for mono(2-ethylhexyl) maleate and their structural similarity to the diesters and maleic acid. This is supported by in silico analysis.

Chemicals in this group are not expected to have carcinogenic or mutagenic potential. The combined information from in vitro tests on dioctyl maleate, diethylhexyl maleate, mono(2-

ethylhexyl) maleate, maleic acid, maleic anhydride and short chain esters, suggests that chemicals in this group are not genotoxic. Carcinogenicity data reported in chronic rat studies did not indicate any potential for maleic acid to induce tumours.

Chemicals mono(2-ethylhexyl) maleate and diethylhexyl maleate may cause specific adverse effects on development based on data for their common metabolite, 2-ethylhexanol (2-EH; CAS No. 104-76-7) that is classified as for developmental toxicity (Safe Work Australia). Further evaluation of data for similar esters of 2-EH is needed to determine classification for developmental toxicity for these chemicals. Based on available data for dioctyl maleate and diethylhexyl maleate (reported as a mixture), and read across information from maleic anhydride, the other chemicals in this group are not expected to be harmful to the reproductive system.

Health hazard classification

These 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 classification for acute toxicity only applies to mono(2-ethylhexyl) maleate (CAS No. 7423-42-9). The classification for corrosion only applies to the monoesters (CAS Nos. 2370-71-0, 2424-62-6, 7423-42-9, 15420-81-2, 30137-97-4, 68186-70-9, 68584-36-1, 68987-59-7). All chemicals in the group should be classified for skin sensitisation.

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 this group indicating that a lower (or higher) classification is appropriate for a specific chemical, that data may be used to amend the default classification for that chemical.

Health hazards	Hazard category	Hazard statement
Acute toxicity	Acute Tox. 4	H302: Harmful if swallowed
Corrosion/irritation	Skin Corr. 1A	H314: Causes severe skin burns and eye damage
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 diester chemicals:

- by direct skin contact during use of cosmetic products
- by incidental skin and eye contact with these chemicals during use of domestic products.

Given the identified health hazards, in particular the observation of sensitisation, the evidence indicates that there is a risk to the public that requires management (see **Recommendation** section). Any risk management measures implemented due to the

sensitisation effects are expected to be sufficient to protect the public from any potential developmental health effects.

Based on the available use information, it is unlikely the public will be exposed to the monoesters in this evaluation.

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 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 (see **Recommendation** section). Control measures implemented due to the local effects are expected to be sufficient to protect workers from any potential developmental health effects.

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 **Recommendation** section.

Further evaluation is required to gather information and evaluate the developmental toxicity of mono(2-ethylhexyl) maleate and diethylhexyl maleate.

Recommendations

Public health

Recommendation to Department of Health

It is recommended that the delegate of the Secretary for Poisons Scheduling list the diester chemicals in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP). This report should be considered together with the report addressing maleic acid esters (short chain).

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

- prohibits, or restricts the concentration of, these chemicals in cosmetic products

- results in labelling requirements that provide warnings of sensitisation and appropriate safety directions.

Consideration should be given to the following:

- that these chemicals are considered to be skin sensitisers with observation of sensitisation reactions in humans.

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 persons conducting a business or undertaking (PCBU) at 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 these chemicals include, but are not limited to:

- 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.

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.

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.

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.

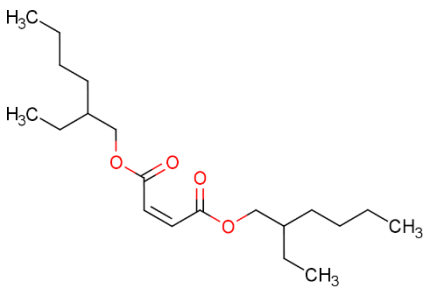
Supporting information

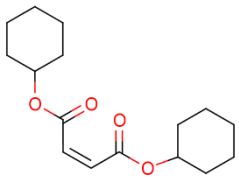
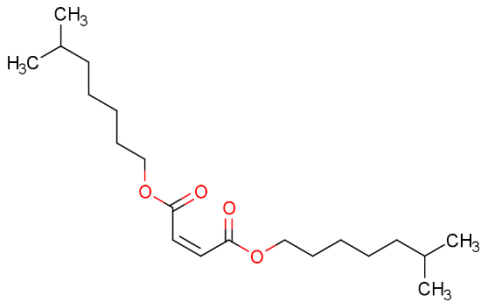
Grouping rationale

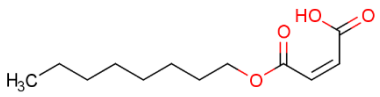
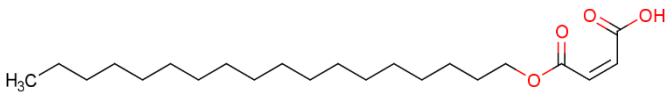
Chemicals in this group are esters of maleic acid with carbon chain length from C6 to C18. Following absorption, maleic esters are hydrolysed to maleic acid and the corresponding alcohol. Systemic toxicity is expected to be driven by maleic acid and the hydrolysis product 2-EH of diethylhexyl maleate and mono(2-ethylhexyl) maleate. Given the close structural similarities of chemicals in this group and their common hydrolysis product (maleic acid), they are expected to have similar systemic toxicological effects; whereas local effects may vary and be dependent on dermal absorption. The monoesters are expected to have properties in between those of the diesters and maleic acid. They are strongly acidic and less hydrophobic than the diesters.

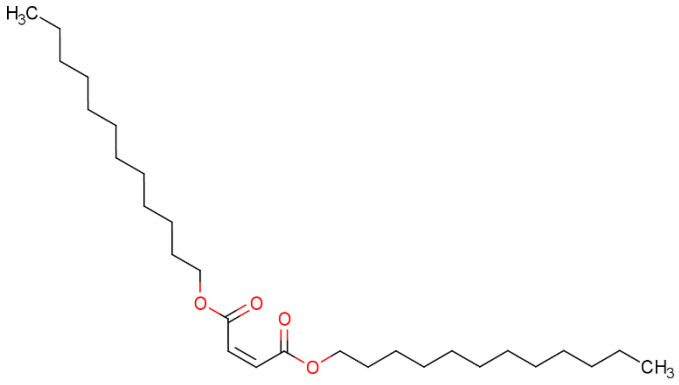
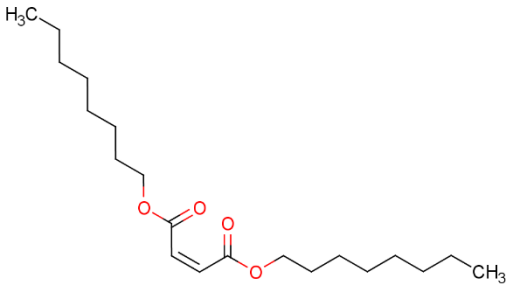
Toxicology information for long chain maleic esters is limited. The available data for maleic anhydride (CAS No. 108-31-6), maleic acid (CAS No. 108-31-6) and short chain maleic acid esters (NICNAS 2015; AICIS2021a; AICIS2021b) are used for chemicals in this group when systemic effects are expected to be caused by maleic acid. Maleic anhydride hydrolyses to maleic acid under aqueous conditions. Therefore, it is considered to be a suitable analogue for systemic effects. The evaluation for short chain maleic acid esters (AICIS2021b) should be read in conjunction with this evaluation.

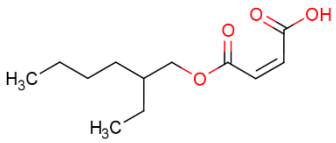
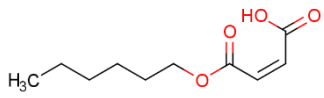
Chemical identity

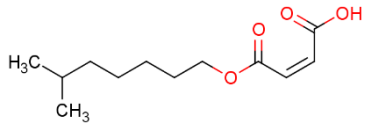
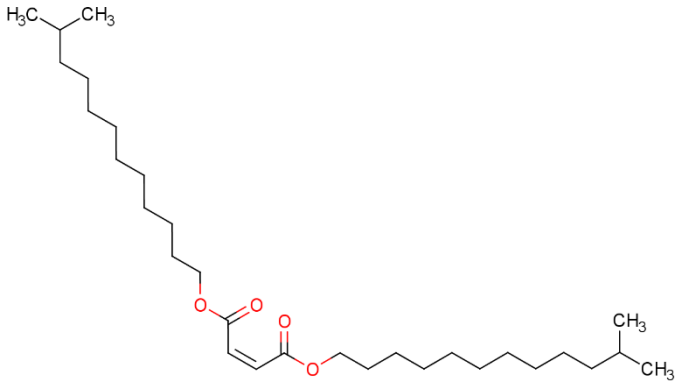
Chemical name	2-Butenedioic acid, (Z)-, bis(2-ethylhexyl) ester
CAS No.	142-16-5
Synonyms	diethylhexyl maleate di(2-ethylhexyl) maleate maleic acid, bis(2-ethylhexyl) ester
Structural Formula	
Molecular Formula	C20H36O4
Molecular Weight (g/mol)	340.5
SMILES	CCCCC(CC)COC(=O)\C=C/C(=O)OCC(CC)CCCC

Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, dicyclohexyl ester
CAS No.	621-13-6
Synonyms	dicyclohexyl maleate maleic acid, dicyclohexyl ester 2-butenedioic acid, (Z)-, bis(cyclohexyl) ester
Structural Formula	
Molecular Formula	C16H24O4
Molecular Weight (g/mol)	280.4
SMILES	C1CCC(CC1)OC(=O)\C=C/C(=O)OC2CCCCC2
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, diisooctyl ester
CAS No.	1330-76-3
Synonyms	diisooctyl maleate maleic acid, diisooctyl ester
Structural Formula	
Molecular Formula	C20H36O4
Molecular Weight (g/mol)	340.5
SMILES	CC(C)CCCCCOC(=O)\C=C/C(=O)OCCCCCC(C)C

Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, monooctyl ester
CAS No.	2370-71-0
Synonyms	maleic acid, monooctyl ester
Structural Formula	
Molecular Formula	C12H20O4
Molecular Weight (g/mol)	228.3
SMILES	CCCCC(CC)COC(=O)\C=C/C(=O)O
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, monooctadecyl ester
CAS No.	2424-62-6
Synonyms	monostearyl maleate maleic acid, monooctadecyl ester octadecyl hydrogen maleate
Structural Formula	
Molecular Formula	C22H40O4
Molecular Weight (g/mol)	368.5
SMILES	CCCCCCCCCCCCCCCCCCCCOC(=O)\C=C/C(=O)O
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, didodecyl ester
CAS No.	2915-52-8
Synonyms	dilauryl maleate

	didodecyl maleate
	maleic acid, didodecyl ester
Structural Formula	
Molecular Formula	C28H52O4
Molecular Weight (g/mol)	452.7
SMILES	CCCCCCCCCCCCOC(=O)\C=C/C(=O)OCCCCCCCCCCCC
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, dioctyl ester
CAS No.	2915-53-9
Synonyms	dioctyl maleate
	dicaprylyl maleate
Structural Formula	
Molecular Formula	C20H36O4
Molecular Weight (g/mol)	340.5
SMILES	CCCCCCCCOC(=O)\C=C/C(=O)OCCCCCCCC
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, mono(2-ethylhexyl) ester

CAS No.	7423-42-9
	mono(2-ethylhexyl) maleate
Synonyms	maleic acid, mono(2-ethylhexyl) ester
	2-ethylhexyl hydrogen maleate
Structural Formula	
Molecular Formula	C12H20O4
Molecular Weight (g/mol)	228.3
SMILES	CCCCC(CC)COC(=O)\C=C/C(=O)O
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, monohexyl ester
CAS No.	15420-81-2
Synonyms	monohexyl maleate
	maleic acid, monohexyl ester
	hexyl hydrogen maleate
Structural Formula	
Molecular Formula	C10H16O4
Molecular Weight (g/mol)	200.2
SMILES	CCCCCCOC(=O)\C=C/C(=O)O
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, monoisooctyl ester
CAS No.	30137-97-4
Synonyms	monoisooctyl maleate
	maleic acid, monoisooctyl ester

	isooctyl hydrogen maleate
	isooctyl maleate (half ester)
Structural Formula	
Molecular Formula	C12H20O4
Molecular Weight (g/mol)	228.3
SMILES	CC(C)CCCCCOC(=O)\C=C/C(=O)O
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, diisotridecyl ester
CAS No.	53817-59-7
Synonyms	diisotridecyl maleate
	maleic acid, diisotridecyl ester
Structural Formula	
Molecular Formula	C30H56O4
Molecular Weight (g/mol)	480.8
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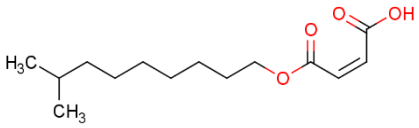
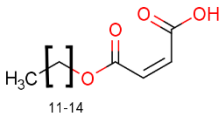
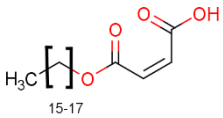
	C)C
Chemical Description	-
Chemical name	2-Butenedioic acid (Z)-, isodecyl ester
CAS No.	68186-70-9

Synonyms	maleic acid, isodecyl ester
Structural Formula	
Molecular Formula	C14H24O4
Molecular Weight (g/mol)	256.3
SMILES	CC(C)CCCCCCCOC(=O)\C=C/C(=O)O
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, mono-C12-15-alkyl esters
CAS No.	68584-36-1
Synonyms	alkyl(C12-15) hydrogen maleate maleic acid, mono-C12-C15-alkyl ester
Structural Formula	
Molecular Formula	unspecified
Molecular Weight (g/mol)	unspecified
SMILES	unspecified
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, mono-C16-18-alkyl esters
CAS No.	68987-59-7
Synonyms	alkyl(C16-18) hydrogen maleate maleic acid, C16-C18-alkyl alcohol monoester
Structural Formula	
Molecular Formula	unspecified

Molecular Weight (g/mol)	unspecified
SMILES	unspecified
Chemical Description	-
Chemical name	2-Butenedioic acid, (Z)-, di-C8-10-alkyl esters
CAS No.	85566-60-5
Synonyms	-
Structural Formula	structure not available
Molecular Formula	unspecified
Molecular Weight (g/mol)	unspecified
SMILES	-
Chemical Description	-

Relevant physical and chemical properties

Chemicals in this group have molecular weights ranging between 200.2 and 480.8 g/mol. The log Kow (calculated with EPI WSKOW) increases with increasing chain length for monoesters from 3.38 to 9.28 and for diesters from 5.75 to 12.85. The acidic pKa (calculated with ACDLabs model) for the monoesters are ~3. The diesters are not acidic. Based on the calculated vapour pressures <0.35 kPa at 20 ºC (calculated with EPI MPBPVP), these chemicals are expected to have low volatility. The estimated dermal absorption values (calculated with EPI DERMWIN) are <0.01 and <0.0003 mg/cm^2/event for mono- and di-esters, respectively. Although this does not take into account ionisation of the monoesters.

Introduction and use

Australia

No information is available on the use of these chemicals in Australia.

International

The following international uses have been identified through the:

- Galleria Chemica
- US National Library of Medicine's Hazardous Substances Data Bank (HSDB)
- European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Substances and Preparations in Nordic countries (SPIN) database; the European Cosmetic Ingredient Database (CosIng)

- Cosmetic Ingredient Review (CIR) report on maleic acid
- Organisation for Economic Cooperation and Development (OECD) Screening Information Dataset (SIDS) Initial Assessment Report (SIAR) on maleic anhydride and maleic acid.

Dioctyl maleate and diethylhexyl maleate have reported cosmetic uses as perfume ingredients and emollients (skin conditioners).

Dioctyl maleate, diethylhexyl maleate and diisotridecyl maleate have reported domestic uses in paints and varnishes.

Didodecyl maleate, diisotridecyl maleate, diethylhexyl maleate and mono(2-ethylhexyl) maleate have reported commercial uses in:

- reprographic agents
- cutting fluids
- lubricants and additives
- fabric and textile products.

Dicyclohexyl maleate, diisooctyl maleate, diethylhexyl maleate and mono(2-ethylhexyl) maleate have reported site limited uses as intermediates in chemical synthesis.

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

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

International regulatory status

No specific controls are currently available for these chemicals.

Human exposure

Workers

During product formulation, dermal, ocular and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment.

Worker exposure to 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.

Public

There is no available information on the use of chemicals in this group in Australia, but dioctyl maleate, diethylhexyl maleate and diisotridecyl maleate have reported use overseas in perfumes (diethylhexyl maleate), skin conditioning products (dioctyl maleate and diethylhexyl maleate); and in paints and varnishes (all 3 chemicals). It is probable that these chemicals have similar uses in Australia. Therefore, the main route of exposure for the general public is expected to be through the skin, and to some extent, by inhalation.

Health hazard information

Toxicokinetics

No data are available for this group of chemicals.

These chemicals have molecular weight ranging between 200.2 and 480.8 g/mol and are expected to be orally available (Lipinski et al. 2001). Based on the calculated log Kow, dermal absorption values and water solubility, the potential dermal absorption of these chemicals is expected to decrease with the increased chain length.

Maleic esters are expected to hydrolyse to maleic acid and relevant long chain alcohols under aqueous conditions. Maleic acid is expected to be the main systemically toxic substance following oral intake of maleic esters. Diethylhexyl maleate and mono(2-ethylhexyl) maleate have the common metabolite, 2-EH. In a non-guideline hydrolysis study with the analogue dibutyl maleate (DBM) (REACHb) a quantitative real-time NMR measurement of DBM in saliva, gastric and intestinal fluids simulants were tested to identify the hydrolysis products of DBM under simulated bodily conditions. The pH of the simulants was 9 (saliva), 1.2 (gastric fluid) and 7.5 (intestinal fluid), respectively. Only in the alkaline saliva simulant (pH = 9) was DBM hydrolysed to the monoester. No hydrolysis was seen at the almost neutral pH of 7.5 or the strongly acidic pH 1.2.

Acute toxicity

Oral

Based on the available data, mono(2-ethylhexyl) maleate has moderate acute toxicity. Dioctyl maleate and diethylhexyl maleate have low acute toxicity following oral exposure. No data are available for the other chemicals in the group. It is likely that the monoesters will in general be more acutely toxic than diesters due to their high acidity damaging the digestive system.

In a non-GLP compliant acute oral toxicity study similar to OECD Test Guideline (TG) 401, Wistar rats (n=10/sex/dose) were treated with 800, 1250, 1600 or 2000 mg/kg bw of mono(2-ethylhexyl) maleate. The reported median lethal dose (LD50) was 1411 mg/kg bw. Reported clinical signs of toxicity included balance disorders and accelerated breathing in abdominal or sternal position at lethal dose (REACHa).

In a GLP compliant acute oral toxicity study conducted in accordance with OECD TG 401, Wistar rats (n=5/sex) were treated with a single dose of 2000 mg/kg bw of the chemical reported as a mixture of dioctyl maleate and diethylhexyl maleate. The LD50 was >2000 mg/kg bw. No clinical signs of toxicity were observed (REACHb).

No data were available to characterise the mixture or to explain why such a mixture was used. It is unclear whether the description as a “mixture” reflects confusion about the common use of “octyl” as a synonym for 2-ethylhexyl.

The following additional LD50 values were reported:

- >5000 mg/kg bw in rats (diethylhexyl maleate; CIR, 2015)
- 14000 mg/kg bw in rats and >20000 mg/kg bw in mouse (diethylhexyl maleate; CCOHS, 1949; CCOHS, 1987)
- 14000 mg/kg bw in rats (dioctyl maleate; CCOHS, 1975).

Dermal

Based on the available data, dioctyl maleate and diethylhexyl maleate have low acute toxicity following dermal exposure. No data are available for other chemicals in the group.

In a non-guideline study, rabbits (n=4/sex/dose) were treated with the chemical reported as a mixture of dioctyl maleate and diethylhexyl maleate. The reported dermal LD50 was 15 mL/kg (equivalent to 14000 mg/kg bw) (REACHb). No other details are available for the study.

The reported LD50 in rabbits is 14000 mg/kg bw. No details on sub-lethal effects are available (CCOHS, 1975).

Corrosion/Irritation

Corrosion

The long chain monoesters are likely to have similar pKa (~3.3, calculated) and titratable acid reserves as the short chain monoesters (AICIS2021b). Therefore, they are expected to be corrosive. This is supported by the data available for mono(2-ethylhexyl) maleate.

In a non-GLP compliant skin irritation study similar to OECD TG 404, 6 Himalayan rabbits were treated with undiluted mono(2-ethylhexyl) maleate on intact and abraded skin for 24 hours under occluded conditions. Observations were recorded at 24, 48, 72 and 96 hours after the patch removal. The following mean scores were reported at 24, 48, 72 and 96 hours: 4, 4, 4 and 4 for erythema and 4, 4, 4 and 4 for oedema respectively (maximum score of 4). The effects were not reversible (REACHa).

Skin irritation

Based on the available data for dioctyl maleate, diethylhexyl maleate and short chain maleic diesters (AICIS2021b), the long chain diesters are not expected to be irritating to skin.

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, 3 Himalayan rabbits were treated with the chemical reported as a mixture of dioctyl maleate and diethylhexyl maleate for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48 and 72 hours, and at 6, 8, 10 and 13 days after patch removal. The

following mean scores were reported for observations at 24, 24 and 72 hours: 2, 2, 2 for erythema and 1.33, 1.33, 1.33 for oedema respectively (maximum score 0 of 4). The erythema was reversible within 8 days and all skin irritation resolved within 13 days (REACHb).

In a non-guideline skin irritation study, 0.5 mL of undiluted diethylhexyl maleate was applied to 6 New Zealand White (NZW) rabbits under occlusion to intact and abraded skin. The skin was observed at 24 and 72 hours after the treatment and the primary irritation index was 1.18. The chemical was reported as non-irritating under the test conditions (CIR 2015).

In a non-guideline primary dermal irritation study, undiluted diethylhexyl maleate was applied to 6 NZW rabbits under occlusion for 24 hours. The primary irritation index was 3.53. The chemical was reported as non-irritating under the test conditions (CIR 2015). No other details are available for the study.

Eye irritation

Based on the available data for dioctyl maleate, diethylhexyl maleate and short chain maleic diesters (AICIS2021b), the long chain diesters are not expected to be irritating to the eye. The monoesters are expected to be corrosive to skin. Corrosive chemicals are also considered to cause irreversible effects on the eyes.

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, 0.1 mL of the chemical reported as a mixture of dioctyl maleate and diethylhexyl maleate was instilled into the conjunctival sac of one eye each of 3 Himalayan rabbits. The eyes were rinsed after 24 hours. The following mean scores were reported at 24, 48 and 72 hours for individual animals: corneal opacity (0/4, 0/4, 0.33/4), iritis (0/2, 0/2, 0/2), conjunctival redness (0.67/3, 0.33/3, 0.67/3) and chemosis (0.33/4, 0.33/4, 0.33/4). Very slight reversible effects were observed in all animals (REACHb).

In a non-guideline eye irritation study, 0.1 mL of undiluted diethylhexyl maleate was applied to one eye of 6 NZW rabbits. The eyes were washed out after 24 hours and observed at 24, 72 hours, 4 and 7 days. The Draize score was 0.3 at 48 hours. The chemical was reported to be non-irritating under the test conditions (CIR 2015).

In a non-guideline eye irritation study, 0.1 mL of undiluted diethylhexyl maleate was applied to one eye of NZW rabbits (n = 6, unwashed; n = 3, washed after 4 seconds). The Draize scores were 2.0 (unwashed) and 0.7 (washed) at 48 and 72 hours. The chemical was reported as non-irritating under the test conditions (CIR 2015).

Sensitisation

Skin sensitisation

Based on the weight of evidence of human, animal and in silico data, and read across information from the short chain maleic esters, the diesters are expected to be skin sensitisers. Limited data are available for the monoesters. Based on data for mono(2-ethylhexyl maleate), structural similarity to the diesters and in silico analysis, the monoesters are expected to be skin sensitisers.

In a GLP compliant guinea pig maximisation test (GPMT) conducted according to OECD TG 406, intradermal induction was performed using the chemical reported as a mixture of dioctyl maleate and diethylhexyl maleate at concentrations 0.1, 1, 5 and 20% in corn oil and dermal

induction with the chemical at 1, 10, 50 and 100% in acetone. Challenge with the chemical at 100% resulted in slight to severe erythema and/or oedema in all the animals. Rechallenge with the chemical at 10% in acetone resulted in similar reactions in all the animals (REACHb).

In an in vivo skin sensitisation study described as being a GPMT, intradermal induction was performed using the chemical reported as a mixture of dioctyl maleate and diethylhexyl maleate at 10% in corn oil, with adjuvant. Challenge with the chemical at 100% resulted in slight to moderate erythema (grade 1 and 2) in 50 and 10% of the animals after 24 and 48 hours, respectively (REACHb). The study summary does not mention a topical induction step, and therefore the validity of this study is unclear.

In a GLP compliant Buehler test conducted according to OECD TG 406, dermal inductions were performed on day 0, 7 and 14 with the chemical reported as a mixture of dioctyl maleate and diethylhexyl maleate at 2.5, 25, 50 and 100% in corn oil. Challenge with the chemical at 25% in corn oil resulted in no skin reactions (REACHb).

In a non-guideline sensitisation test in guinea pigs (n=12) treated with 100% diethylhexyl maleate, slight erythema was observed during induction (2 sites after the sixth dose) and no skin reaction was observed in challenged animals (CIR, 2015). No other details are available for the study.

In a GLP compliant GPMT conducted according to OECD TG 406, intradermal induction was performed using 5% mono(2-ethylhexyl) maleate in polyethylene glycol 300 (PEG 300), and dermal induction with the chemical at 15% in PEG 300. Challenge with 10% mono(2-ethylhexyl) maleate in PEG 300 resulted in erythema (grade 1) in 80 and 60% of the animals after 24 and 48 hours, respectively (REACHa).

In silico data

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 was utilised to estimate the skin sensitisation potential of the monoesters. An alert for skin sensitisation by alpha,beta-unsaturated esters was reported. Alpha,beta-unsaturated esters are electrophilic compounds that are known to undergo Michael-type conjugate additions with nucleophiles. Therefore, they are likely to interact with skin proteins by such a mechanism. The predicted effective concentration for a 3 fold increase in lymphocyte proliferation in local lymph node assay (LLNA EC3) for monohexyl maleate, mono(2-ethylhexyl) maleate, monoisooctyl maleate, monooctyl maleate, isodecyl maleate, lauryl maleate, alkyl (C16-18) hydrogen maleate and monostearyl maleate were 0.52, 0.56, 0.58, 0.60, 0.66, 0.71–0.82, 0.89–0.97 and 0.97% respectively, indicating strong sensitisation potential.

Observation in humans

In a human patch test, dioctyl maleate at 0, 1, 2, 4, 5 and 10% in petrolatum or a leave on cosmetic product was applied to 18 female subjects. Positive reactions were observed in 10 subjects treated with 5 or 10% concentrations of the chemical at day 4. Additional tests were conducted using aged dioctyl maleate at 0.2, 1, 2, 5 and 10% in petrolatum; 9 out of 10 subjects tested were positive at 5 or 10%. No allergic reactions were observed at lower concentrations (<5%) for these chemicals used in this study (Lotery et al. 2007).

Repeat dose toxicity

Oral

Based on the available data for dioctyl maleate and diethylhexyl maleate (reported as a mixture), and for maleic acid and maleic anhydride (AICIS2021a; NICNAS 2015), chemicals in this group are not expected to cause severe adverse effects following repeated oral exposure. The liver and kidney effects are not sufficiently severe to warrant hazard classification.

In a GLP compliant combined repeated dose toxicity test with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422, Wistar rats (n=10/sex/dose) were administered with the chemical reported as a mixture of dioctyl maleate and diethylhexyl maleate by gavage once daily at 30, 300 and 1000 mg/kg bw/day for a total of 29 days (males) and up to 55 days (females). No mortality or treatment related clinical signs of toxicity were reported. Liver and kidney weights (absolute and relative) were increased at 300 and 1000 mg/kg bw/day. No histopathological changes were observed. A NOAEL of 300 mg/kg bw/day was reported based on significant liver and kidney effects observed at 1000 mg/kg bw/day (REACHb).

In a GLP compliant test combined repeated dose toxicity with the reproduction/developmental toxicity screening test conducted similarly to OECD TG 422, female Wistar rats (n=3/dose) were administered with the chemical reported as a mixture of dioctyl maleate and diethylhexyl maleate by gavage once daily at 500 or 1000 mg/kg bw/day for 10 days. No mortality and no treatment related clinical signs of toxicity were reported. Liver weights were increased; however, histopathology was normal (REACHb).

Dermal

No data are available for this group of chemicals.

Inhalation

No data are available for this group of chemicals.

Genotoxicity

Based on the available data for dioctyl maleate and diethylhexyl maleate (reported as a mixture), maleic anhydride, maleic acid and short chain esters (NICNAS 2015; AICIS2021a; AICIS2021b), chemicals in this group are not expected to be genotoxic. The cyclic hydrolysis alcohol metabolite cyclohexanol (CAS No. 108-93-0) of the chemical dicyclohexyl maleate (CAS No. 621-13-6) was not genotoxic (REACHc).

In vitro

Negative results were reported in the following in vitro genotoxicity studies for the chemical reported as a mixture of dioctyl maleate and diethylhexyl maleate (REACHb):

- a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, with and without metabolic activation (S9) at concentrations of 8–5000 µg/plate

- a chromosome aberration study (OECD TG 473) in Chinese hamster lung cells (V79) with and without metabolic activation at concentrations 5–500 µg/mL
- a mammalian cell gene mutation study (OECD TG 476) in the thymidine kinase (TK) locus in mouse lymphoma L5178Y cells with and without metabolic activation at concentrations 1–100 µg/mL.

Negative results were reported for mono(2-ethylhexyl) maleate in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and *Escherichia coli* WP2 uvr A, with and without metabolic activation (S9) at concentrations of 4–10000 µg/plate (REACHa).

Negative results were reported in the following in vitro and in vivo genotoxicity studies for cyclohexanol (REACHc; NTP 1983):

- a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium strains* TA 1535, TA 1537, TA 1538, TA 98 and TA100 with and without metabolic activation (S9) at concentrations up to 10000 µg/plate
- a mammalian cell gene mutation assay (OECD TG 476) in the TK locus in mouse lymphoma cells L5178Y with and without metabolic activation at concentrations up to 1000 µg/mL
- a mammalian erythrocyte micronucleus test (OECD TG 474) in NMRI mice (n=5/sex/dose) treated with 500, 1000 and 1500 mg/kg bw concentrations by gavage.

Carcinogenicity

No data are available for these chemicals. Based on data for maleic anhydride and maleic acid (AICIS2021a; NICNAS 2015), these chemicals are not expected to have carcinogenic potential.

Reproductive and development toxicity

Based on the available data for their common metabolite 2-EH, mono(2-ethylhexyl) maleate and diethylhexyl maleate may cause specific adverse effects on the reproductive system. The alcohol hydrolysis product 2-EH of these 2 chemicals is a known reproductive toxin (HCIS; NICNAS 2016). Based on the data for dioctyl maleate and diethylhexyl maleate (reported as a mixture), and data for maleic anhydride, maleic acid and short chain maleic acid diesters (AICIS2021a; AICIS2021b; NICNAS 2015), the other chemicals in this group are not expected to cause specific adverse effects on fertility, sexual function or development following oral exposure.

In a GLP compliant combined repeated dose toxicity with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422 (see Repeat dose toxicity), Wistar rats (n=10/sex/dose) were administered with the chemical reported to be a mixture of dioctyl maleate and diethylhexyl maleate by gavage once daily at 30, 300 or 1000 mg/kg bw/day, from 14 days before mating for a total of 29 days (males) or up to 55 days (females). No toxicologically relevant effects on reproductive, gestational or developmental effects were observed (REACHb). While no effects were reported in this study, the hydrolysis product of diethylhexyl maleate, 2-EH, has been assessed by the Scheme and is classified as a reproductive toxin (NICNAS 2016). Based on the proportion of 2-EH formed on hydrolysis of the esters, equivalent doses of the esters required to reach the level of toxicity reported for 2-EH (NOAEL of 130 mg/kg bw/day), are 170–340 mg/kg bw/day for diethylhexyl maleate (depending on extent of hydrolysis) and 228 mg/kg bw/day for mono(2-ethylhexyl) maleate.

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