Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Maleic acid esters (short chain)

Evaluation statement

14 September 2021

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AICIS Evaluation Statement

Subject of the evaluation

Maleic acid esters (short chain).

Chemicals in this evaluation

Name	CAS registry number
2-butenedioic acid, (Z)-, dibutyl ester	105-76-0
2-butenedioic acid, (Z)-, diethyl ester	141-05-9
2-butenedioic acid, (Z)-, dimethyl ester	624-48-6
2-butenedioic acid, (Z)-, mono(1-methylethyl) ester	924-83-4
2-butenedioic acid, (Z)-, monobutyl ester	925-21-3
2-butenedioic acid, (Z)-, monomethyl ester	3052-50-4
2-Butenedioic acid, (Z)-, monoethyl ester	3990-03-2
2-butenedioic acid, (Z)-, bis(2-methylpropyl) ester	14234-82-3
2-butenedioic acid, (Z)-, mono(1,1-dimethylethyl) ester	45022-27-3

Reason for the Evaluation

The Evaluation Selection Analysis indicated potential risks to human health.

Parameters of evaluation

A human health risk assessment for all identified industrial uses of the chemicals in this group of structurally similar maleic esters. These chemicals have been assessed as a group as they have a common metabolite (maleic acid) and are expected to have similar bioavailability.

Summary of evaluation

Summary of introduction, use and end use

There is currently no information about the use and volume of use of this group of chemicals in Australia.

Based on international information, these chemicals are used in a wide range of industrial applications, in domestic products (coatings, adhesives, inks, toners and colouring agents), in commercial products (construction materials and reprographic agents), as an intermediate in chemical manufacturing and monomers in plastic production. The chemicals have non-industrial application, as flavourings in the food industry.

The diesters are used in cosmetic products (as plasticisers, emollients, solvents and fragrance ingredients). No information on concentrations in use could be identified.

Human health

Summary of health hazards

The critical health effects for risk characterisation include:

- systemic acute effects from oral exposure
- local effects [skin sensitisation, and corrosivity (monoesters only)]
- systemic effects following repeated oral exposure.

The limited available information on maleic esters and analogues suggest that the chemicals are readily absorbed via 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 diesters are expected to have low acute toxicity except for dimethyl maleate that has moderate acute toxicity via the oral route. The limited available data for the diesters suggest that all they have low dermal and inhalation toxicity. No data are available for the monoesters.

The diesters are not irritating to skin or eyes. Based on data for butyl hydrogen maleate and physico chemical properties, the monoesters 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. This is supported by observations in humans where sensitisation reactions were reported in human patch test studies at concentrations of 0.1%. There are no skin sensitisation data available for the monoesters. However, the chemicals in this group are considered to be skin sensitisers based on their structural similarity to the diesters and maleic acid (classified as a sensitiser in the HCIS) and in silico analysis.

The chemicals are not expected to cause any severe systemic effects; however, repeated oral intake of high doses of the chemicals may cause renal changes. Dose-dependent renal effects were observed in oral repeated dose toxicity studies with butyl hydrogen maleate and dibutyl maleate. No kidney effects were reported in a repeated dose toxicity study with dimethyl maleate. Similar to maleic acid, the kidney effects are more prominent at doses higher than 100 mg/kg bw day. Data are insufficient to warrant hazard classification for specific target organ toxicity (repeated exposure) for maleic esters.

The chemicals in this group are not expected to have carcinogenic, mutagenic or reproductive toxicity potential. The combined information from in vitro and in vivo tests for chemicals, maleic acid and maleic anhydride, suggests that the chemicals are not genotoxic.

Carcinogenicity data from chronic rat studies did not indicate any potential for maleic acid to induce tumours. The available data for dibutyl maleate, butyl hydrogen maleate, dimethyl maleate and maleic anhydride indicated negative results in reproductive toxicity and developmental toxicity studies.

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 classification for acute toxicity – oral only applies to dimethyl maleate (CAS No. 624-48-6). The classification for corrosion only applies to the monoesters (CAS Nos. 925-21-3, 45022-27-3, 924-83-4, 3052-50-4, 3990-03-2). 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 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	Category 4	H302: Harmful if swallowed
Corrosion	Category 1	H314: Causes severe skin burns and eye damage
Skin sensitisation	Category 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 chemicals:

- by direct skin contact during use of cosmetic products (diesters)
- by incidental skin and eye contact with these chemicals during use of domestic products
- by inhaling aerosols.

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

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 the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term, systemic acute and local health effects, the chemicals in this group 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).

Conclusions

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

Recommendations

Public health

Recommendation to the Department of Health

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

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, the chemicals in cosmetic products
- results in labelling requirements that provide warnings of sensitisation and appropriate safety directions.

Consideration should be given to the following:

- the chemicals are skin sensitisers with observation of sensitisation reactions in humans at low concentrations
- the monoesters are corrosive to skin

- internationally, diethyl maleate is prohibited for use as a fragrance ingredient based on the sensitising potential (see supporting information).

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.

Advice to industry

The information in this report, including recommended hazard classifications, should be used by persons conducting a business or undertaking at workplace (such as an employer) to determine the appropriate controls.

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

- using local exhaust ventilation to prevent the 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 the chemicals.

These control measures should be supplemented with:

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

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

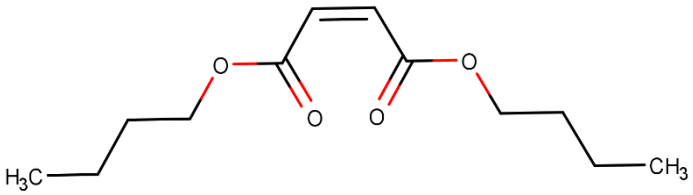
Grouping rationale

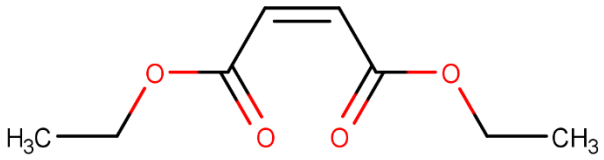
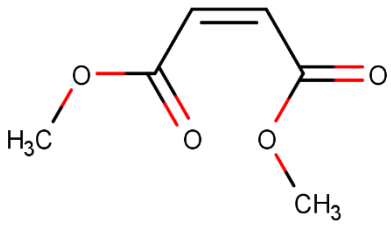
The chemicals in this group are mono and diesters of maleic acid with carbon chain length up to C4. Following absorption, maleic esters are hydrolysed to maleic acid and the corresponding alcohol. Systemic toxicity is expected to be driven by maleic acid. Given the close structural similarities of the chemicals in this group and that they have a 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.

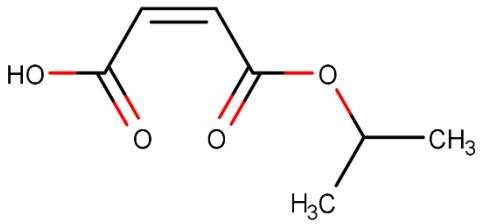
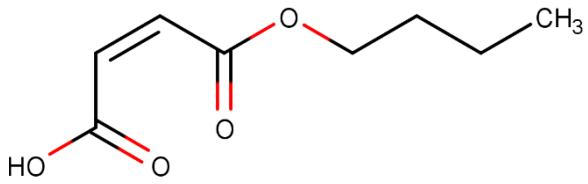
Toxicology information for short chain maleic esters is limited. The available data for maleic acid (CAS No. 108-31-6) and maleic anhydride (CAS No. 108-31-6) are used for the other chemicals in this group when systemic effects are expected to be caused by maleic acid. Maleic anhydride hydrolyses to maleic acid under aqueous conditions and is; therefore, considered to be a suitable analogue for systemic effects.

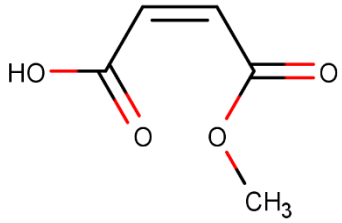
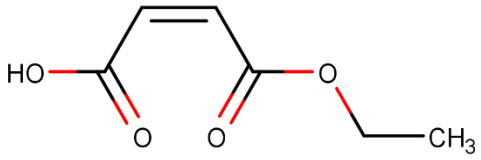
Acrylic esters with similar physicochemical properties to the maleic esters are used to estimate dermal absorption.

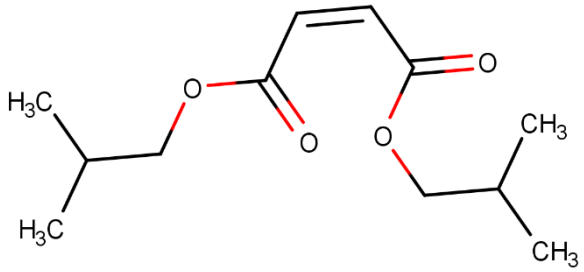
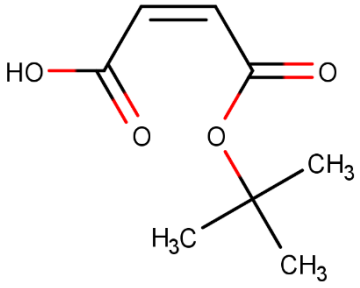
Chemical identities

CAS number	105-76-0
Synonyms	dibutyl maleate maleic acid, dibutyl ester 2-butenedioic acid (2*Z*)-, 1,4-dibutyl ester
Structural Formula	
Molecular Formula	C12H20O4
Molecular Weight (g/mol)	228
SMILES	O=C(OCCCC)C=CC(=O)OCCCC
Chemical Description	N/A
CAS number	141-05-9

Synonyms	diethyl maleate maleic acid, diethyl ester 2-butenedioic acid (2*Z*)-, 1,4-diethyl ester
Structural Formula	
Molecular Formula	C8H12O4
Molecular Weight (g/mol)	172.2
SMILES	O=C(OCC)C=CC(=O)OCC
Chemical Description	N/A
CAS number	624-48-6
Synonyms	dimethyl maleate maleic acid, dimethyl ester 2-butenedioic acid (2*Z*)-, 1,4-dimethyl ester
Structural Formula	
Molecular Formula	C6H8O4
Molecular Weight (g/mol)	144.1
SMILES	O=C(OC)C=CC(=O)OC
Chemical Description	N/A
CAS No	924-83-4
Synonyms	monoisopropyl maleate

Structural Formula	maleic acid, isopropyl ester 2-butenedioic acid (2Z)-, 1-(1-methylethyl) ester 
Molecular Formula	C7H10O4
Molecular Weight (g/mol)	158.2
SMILES	O=C(O)C=CC(=O)OC(C)C
Chemical Description	N/A
CAS number	925-21-3
Synonyms	hydrogen butyl maleate maleic acid monobutyl ester 2-butenedioic acid (2Z)-, 1-butyl ester
Structural Formula	
Molecular Formula	C8H12O4
Molecular Weight (g/mol)	172.2
SMILES	O=C(O)C=CC(=O)OCCCC
Chemical Description	N/A
CAS number	3052-50-4
Synonyms	methyl hydrogen maleate maleic acid, methyl ester 2-butenedioic acid (2Z)-, 1-methyl ester monomethyl maleate

Structural Formula	
Molecular Formula	C5H6O4
Molecular Weight (g/mol)	130.1
SMILES	O=C(O)C=CC(=O)OC
Chemical Description	N/A
CAS No	3990-03-2
Synonyms	ethyl hydrogen maleate maleic acid, ethyl ester 2-butenedioic acid (2Z)-, 1-ethyl ester monoethyl maleate
Structural Formula	
Molecular Formula	C6H8O4
Molecular Weight (g/mol)	144.13
SMILES	O=C(O)C=CC(=O)OCC
Chemical Description	N/A
CAS Number	14234-82-3
Synonyms	diisobutyl maleate maleic acid, diisobutyl ester 2-butenedioic acid (2Z)-, 1,4-bis(2-methylpropyl) ester

Structural Formula	
Molecular Formula	C12H20O4
Molecular Weight (g/mol)	228.3
SMILES	O=C(OCC(C)C)C=CC(=O)OCC(C)C
Chemical Description	N/A
Cas number	45022-27-3
Synonyms	tert-butyl maleate 2-butenedioic acid (2Z)-, 1-(1,1-dimethylethyl) ester
Structural Formula	
Molecular Formula	C8H12O4
Molecular Weight (g/mol)	172.2
SMILES	O=C(O)C=CC(=O)OC(C)(C)C
Chemical Description	N/A

Relevant physical and chemical properties

The chemicals in this group have molecular weights ranging between 130–228 g/mol. The log Kow is expected to increase with increasing chain length for mono- and diesters, respectively. The acidic pKa for the monoesters is approximately 3. The diesters are not acidic. Based on the reported experimental vapour pressures below 0.5 kPa the chemicals are expected to have low volatility.

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 Galleria Chemica, the 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), the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary, the European Food Safety Authority (EFSA), and the Organisation for Economic Cooperation and Development (OECD) Screening Information Dataset (SIDS) Initial Assessment Report (SIAR) on dibutyl maleate.

The chemicals have reported cosmetic uses as:

- fragrance ingredients (dibutyl and diethyl maleate)
- solvents (dibutyl and dimethyl maleate)
- skin conditioners (dimethyl and diisopropyl maleate)
- plasticisers (diisopropyl maleate).

Reported domestic uses includes uses in inks and toners (hydrogen butyl maleate) and the following uses for dibutyl maleate in:

- paints, lacquers and varnishes
- adhesives and binding agents
- fillers
- surface treatments
- colouring agents.

Dibutyl maleate has reported commercial uses in:

- construction materials
- reprographic agents
- adhesive and binding products
- textile dyeing and finishing products.

The chemicals have reported site-limited uses in:

- plasticisers
- chemical synthesis
- copolymers.

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

None of the chemicals in this group are classified as hazardous.

Exposure standards

Australian

No exposure standards are available for the chemicals in Australia.

International regulatory Status

European Union

Diethyl maleate is listed in the EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products. It was the recommendation of the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) that these substances should not be used as fragrance ingredients in cosmetic products (SCCNFP, 2000)

Canada

Diethyl maleate is listed on Canada's Cosmetic Ingredient Hotlist - List of Ingredients that are Prohibited for Use in Cosmetic Products.

Asia

Diethyl maleate is listed in the ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

Other

Diethyl maleate is listed as prohibited in the International Fragrance Association (IFRA) Standards (40th amendment). The Expert Panel for Fragrance Safety reviewed all the available data for diethyl maleate and recommends not to use diethyl maleate as or in fragrance ingredients in any finished product application (IFRA, 2006).

Exposure standards

No exposure standards are available for the 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 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.

Public

There is no available information on potential uses of the chemicals in this group in Australia, but some of the chemicals are reported to be used overseas in cosmetic products, coatings, adhesives, inks and toners. It is probable that the 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

Limited data are available for the chemicals.

The chemicals have low molecular weight and log Kow values below 5. Therefore, the chemicals are expected to be orally bioavailable (Lipinski et al., 2001). Based on data for diethyl maleate and structurally related chemicals, the diesters are expected to be readily absorbed through the skin. Absorption of the monoesters is expected to be higher than maleic acid but lower than the diesters. This assumption is based on the physicochemical properties of the maleic monoesters. They have log Kow values which are lower than the diesters, but higher than maleic acid.

In a study in humans, approximately 50% of diethyl maleate was absorbed through skin. In the study, 6 volunteers received a single topical application of radiolabelled diethyl maleate in acetone (chemical dose = 4µg/cm^2). A Hill chamber covered the site for 24 hours. Radioactivity excreted in urine (corrected with a parenteral correction factor) was used to calculate dermal absorption (Bronaugh et al., 1990).

In a study using pig skin, the structurally related chemicals butyl acrylate (CAS No. 141-32-2) and methyl methacrylate (CAS No. 80-62-6) were considered to have moderate to very high skin permeability. The permeability was concentration dependent and increased with decreasing concentration of the chemicals (Schenk et al., 2018).

Dermal penetration studies of acrylic acid esters (acrylates) demonstrated that rat skin penetration declined with increased molecular weight and log Kow. The presence of carboxylesterases in the skin was demonstrated by the appearance of methyl acrylic acid in the receptor fluid after passage through rat skin (Gelbke et al., 2018).

Maleic esters and maleic anhydride are expected to be hydrolysed to maleic acid and the relevant alcohols under aqueous conditions. Maleic acid is expected to be the main systemically toxic substance following oral intake of maleic esters.

Following oral administration of maleic anhydride to dogs at 60 mg/kg bw/day for 90 days, the plasma levels were measured. The elimination rate constant of maleic anhydride was calculated to be 0.083/day, assuming a one-compartment model. (NICNAS IMAP, 2015).

Acute toxicity

Oral

Based on the available data, dimethyl maleate has moderate acute toxicity. Diethyl and dibutyl maleate are expected to have low acute oral toxicity. No data are available for the other chemicals in the group.

The following median lethal dose (LD50) values were reported:

- >3730 mg/kg bw in a non-guideline study in rats (dibutyl maleate, REACH)
- >3200 mg/kg bw in a non-guideline study in rats (diethyl maleate, REACH)
- 1340–1909 mg/kg bw in rats (dimethyl maleate, REACH, RTECS).

Dermal

Based on the available data, diethyl and dibutyl maleate have low acute dermal toxicity. No information is available for the other chemicals in this group.

In a GLP compliant acute dermal toxicity study conducted in accordance with OECD Test Guideline (TG) 402, Sprague Dawley (SD) rats (5/sex) were treated with a single dose of dibutyl maleate. The LD50 was >2000 mg/kg bw. Sub-lethal effects include erythema (redness) and chromodacryorrhoea (bloody tears) (REACHa). Another study with limited details reported an LD50 of 9880 mg/kg bw under occlusive conditions with 4 male New Zealand White (NZW) rabbits (REACHa).

In a GLP compliant acute dermal toxicity study conducted in accordance with the OECD TG 402, Wistar rats (5/sex) were treated with a single dose of dibutyl maleate. The LD50 was >2000 mg/kg bw. Sub-lethal effects include erythema and necrosis (REACH). In a non-GLP compliant non-guideline study with limited information, the chemical was applied to the clipped skin of 4 male NZW rabbits for 24 h under occlusive conditions. The reported LD50 was 609 mg/kg bw (REACHa).

In a GLP compliant acute dermal toxicity study conducted in accordance with the OECD TG 402, Wistar rats (5/sex/dose) were treated with dimethyl maleate 500 and 2000 mg/kg bw for 24 hours under occlusive conditions followed by 14 days of observation. No mortalities were reported. Sublethal effects included local erythema followed by necrosis in both treatment groups. The reported LD50 was >2000 mg/kg bw (REACHc).

Studies with limited information reported the following LD50 values for diethyl maleate:

- >2500 mg/kg bw in rats (REACHb)
- 5000 mg/kg in rats (RTECS)
- 4600 mg/kg bw in rabbits (RTECS)
- 5750 mg/kg bw in rats (REACHb).

Inhalation

Based on the available data, dibutyl malelate has low acute inhalation toxicity. No or limited information is available for the other chemicals in the group.

A median lethal concentration (LC50) of >5 mg/L was reported based on a GLP compliant acute inhalation study conducted in accordance with OECD TG 403, in which SD rats (5/sex) were exposed to dibutyl maleate as an aerosol (nose only) for 4 hr at 5 mg/L. No mortalities were reported. Small haemorrhages were reported in the lungs of 7 of the animals (REACHa).

Inhalation studies with limited information reported:

- LC50 >1 mg/L, rats (species unspecified), saturated diethyl maleate vapours, 8 hours
- LC50 was not determined, no mortalities occurred following a 4 hour exposure of albino rats (6/sex) to concentrated dimethyl maleate vapours.

Observation in humans

No data are available on effects following acute exposure in humans.

Corrosion/Irritation

Corrosion

Based on an in vitro guideline study, butyl hydrogen maleate is corrosive. The other monoesters are likely to have similar pKas and titratable acid reserves as butyl hydrogen maleate; therefore, all the monoesters are expected to be corrosive.

In a GLP compliant in vitro skin corrosion assay study conducted in accordance with OECD TG 431, butyl hydrogen maleate was applied to reconstructed human epidermis (EPISKIN^{TM}) for 3, 60 and 240 minutes. The mean tissue viability was 75.4%, 10.6% and 5.8% min after 3, 60 and 240 minutes respectively. Substances that reduce viability to <35% after 3, 60 or 240 minutes exposure are classified as corrosive. Therefore, the chemical is considered to have potential to cause corrosion in vivo following application to skin (REACHd).

Skin Irritation

Based on the available data from animal guideline studies, the diesters are not irritating to skin. Low concentrations (below 4%) are not expected to be irritating to humans.

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, 3 female NZW rabbits were treated with dibutyl maleate as a single dermal dose of 0.5 mL. Observations were made over 8 days after patch removal. The following mean scores for individual animals were reported (maximum score of 4): 1.3, 0.7 and 0.7 for erythema and 0, 0 and 0 for oedema. All signs of irritation resolved within 8 days. Supporting studies found the chemical was slightly irritating to rats but not to mice or rabbits (REACHa).

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, 3 female NZW rabbits were treated with diethyl maleate for 4 hours under semi-occlusive conditions. Observations were recorded at 1, 24, 48 and 72 hours after patch removal. The following mean scores for individual animals were reported (maximum score of 4): 0.3, 0.0 and 0.9 for erythema and 0, 0 and 0 oedema. Signs of slight irritation resolved within 24 hours (REACHb).

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, 3 female albino rabbits were treated with dimethyl maleate for 4 hours under semi-occlusive conditions. Observations were recorded at 1, 24, 48 and 72 hours after patch removal. The following mean scores for individual animals were reported (maximum score of 4): 0.0, 0.0 and 0.0 for erythema. In a similar GLP compliant study, NZW rabbits (3/sex) were treated with the chemical under occlusive conditions and the reported scores for individual animals were 0, 0, 0, 0, 0, 0.3 for erythema and 0.3, 0, 0, 0, 0, 0 for oedema. All symptoms resolved within 48 hours of the end of the exposure period (REACHc).

Eye Irritation

Based on the available data from animal guideline studies, the diesters are not irritating to the eye. Based on the available data, butyl hydrogen maleate is 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 dibutyl maleate was instilled into one eye each of 3 rabbits (sex/species not reported) and observed for 3 days. Scores for individual animals one hour after application were reported: animal 1 (conjunctival redness 2/2, chemosis 1/1), animal 2 (conjunctival redness 1/2) and animal 3 (corneal opacity 1/2). All reactions resolved within 2 days of treatment (REACH). In another study, dibutyl maleate was applied to the eyes of rabbits (number, sex, strain not reported). After one hour all animals had a slight conjunctival hyperaemia that disappeared after 24 hours (OECD SIDS, 2002).

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, 0.1 mL diethyl maleate was instilled into one eye each of 3 female NZW rabbits. The following mean scores were reported at 24, 48 and 72 hours for individual animals: corneal opacity (0/4, 0/4, 0/4), iritis (0/2, 0/2, 0/2), conjunctival redness (0.3/3, 0.3/3, 0.7/3) and chemosis (0/4, 0/4, 0/4). Very slight to conjunctival redness was observed in all animals with a maximum score of 2 lasting a maximum of 48 hours. Ocular lesions were reversible in all animals within 72 hours (REACHb).

In an eye irritation study conducted in accordance with OECD TG 405, 0.1 mL diethyl maleate was instilled into one eye each of 3 male NZW rabbits for 24 hours. The following mean scores were reported at 24, 48 and 72 hours for individual animals: corneal opacity (1.7/4, 1/4, 1/4,), iritis (0.3/2, 0.3/2, 0/2), conjunctival redness (2/3, 1.7/3, 1.3/3) and chemosis (1/4, 0.7/4, 0.7/4). All effects resolved within 7 days of application. In a similar study, diethyl maleate was applied to the eyes of 2 NZW rabbits (sex not reported).

Observations were made at 1, 24 and 48 hours. The following mean scores were reported at 24 and 48 hours for individual animals: corneal opacity (0/4, 0/4), iritis (0/2, 0/2), conjunctival redness (2/3, 2/3) and chemosis (1/4, 1/4). All symptoms resolved within 5 days (REACHb).

Observation in humans

Diethyl maleate was not irritating to humans when applied at 4% in petrolatum for 48 hours in an occlusive closed-patch test. Dibutyl maleate (0.2–0.3 mL) was applied to the skin on the inner side of the forearm of one man. After 13–15 minutes the subject reported slight burning and prickling and the test area was red. The erythema covered an area of 15–20 cm^2 at 30–60 minutes after exposure and the burning and prickling disappeared (OECD SIDS, 2002).

Sensitisation

Based on the available animal and human health data the maleic acid diesters are considered to be skin sensitisers. There are no skin sensitisation data available for the monoesters. Based on structural similarity to the diesters and in silico analysis, the monoesters are expected to be skin sensitisers; however, their potency will be dependent on dermal absorption.

In a guinea pig maximisation test (GPMT) conducted according to OECD TG 406, intradermal induction was performed using 5.0% diethyl maleate in corn oil and dermal induction with 100% of the chemical. The animals challenged with 25% diethyl maleate in acetone resulted in reactions in 95% of the animals (REACHb).

In two local lymph node assays (LLNAs) with limited information available, the reported stimulation indices (SI) were 2.1, 3.3, 3.5, 7.5, 16.0 for concentrations of 1.0, 2.5, 5.0, 10.0, 25.0, respectively in the first study and 16.3, 22.6, 13.1 for concentrations of 25.0, 50.0, 100.0 in the second study. The reported concentration producing a three-fold increase in lymphocyte proliferation (EC3) was 2% in the first study and 5.8% in the second study, indicating moderate sensitisation potential for diethyl maleate (Gerberick et al., 2005).

In a non-GLP compliant GPMT similar to OECD TG 406, intradermal and dermal induction was performed with 1% of dimethyl maleate in ethanol. Challenge with 1% dimethyl maleate in ethanol resulted in slight to moderate erythema in all of the animals (REACHc).

In a non-GLP compliant GPMT similar to OECD TG 406, intradermal induction was performed using 10% dibutyl maleate in corn oil. The animals challenged with 100% dibutyl maleate resulted in erythema (grade 1 and 2) in 80% of the animals (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 LLNA EC3 for monobutyl maleate, monoethyl maleate and monomethyl maleate, mono methylethyl maleate, and mono

dimethylethyl maleate were 0.4, 1.6, 2.0, 2.3, 2.5% respectively, indicating moderate to strong sensitisation potential.

Observation in humans

In a maximisation test in 25 volunteers, 4% of diethyl maleate in petrolatum produced reactions in all volunteers (Monographs on Fragrance Raw Materials, 1979). No further information is available.

In a patch test study in patients suspected of suffering from contact sensitisation to cosmetics, 3.2% of 182 patients displayed a positive reaction to diethyl maleate (0.1% in petrolatum) (SCCS, 2012).

In a patch test study in patients with suspected furniture-related dermatitis caused by dimethyl fumarate, reactions to diethyl maleate (0.0012– 0.12%) were observed in 21/37 patients at 0.12% and reactions to dimethyl maleate (0.001–1%) in 9/9 of patients tested at 1%. The patients with a strong response to low concentrations of dimethyl fumarate had multiple concurrent reactions to diethyl maleate, and dimethyl maleate, suggesting cross-sensitisation (Lammintausta et al., 2010).

In an envelope making factory, 50% of the workers exposed to envelope glue developed contact dermatitis. In a subsequent patch test, 10/11 workers had a positive reaction to dibutyl maleate (10% in acetone). After the workers stopped making the envelopes, their dermatitis resolved (REACHa).

Repeat dose toxicity

Oral

Based on the available data, the chemicals do not cause severe adverse effects following repeated oral exposure. While renal effects were observed in the majority of the studies, the effects were not severe enough to warrant hazard classification.

In a GLP compliant 90 day study conducted in accordance with OECD TG 408, SD rats (15/sex/dose) were administered dibutyl maleate by gavage at 30, 95, 300 mg/kg bw/day daily for 90 days followed by a 2 week treatment free recovery period. No treatment related effects were found in clinical observations, body weights, food consumption, ophthalmic examinations, functional observational battery assessments, haematological parameters, coagulation and urinalysis during the dosing or recovery period. Increased kidney weights were found in males and females at the highest dose and were also observed in males at the end of the recovery period. This correlated histologically to chronic progressive nephropathy (CPN) and with tubular basophilia (elevated numbers of white blood cells) within the renal cortex. Renal lesions included minimal to moderate CPN, mineralisation at the corticomedullary junction and/or medulla, tubular basophilia within the cortex, and tubular ectasia (expansion of tubular structures) in the cortex and/or medulla. The moderate renal effects were mainly seen in animals receiving the highest dose; at the other doses effects were minimal to mild. Some of the effects persisted in animals receiving the highest dose (no further information available). The no observed adverse effect level (NOAEL) was 95 mg/kg bw/day based on the renal effects at 300 mg/kg bw/day (REACHa).

In a GLP compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422, Wistar rats (12/sex/dose) were administered butyl hydrogen maleate by gavage once daily at 30, 100 and 175 mg/kg bw/day for a total of 42 days (males) and up to 55 days (females). No treatment related mortality was reported. A few animals in the highest and mid dose groups had increased salivation and noisy respiration. No other clinical signs of toxicity were reported. No treatment related macroscopic abnormalities were reported. Blood chemistry was normal apart from an increase in bile acids in males of the highest dose group. Increased absolute and relative liver weights were reported for males in the mid and high dose groups and for all females liver histopathology analyses showed hepatocellular hypertrophy in all groups, single cell death of hepatocytes and increased incidence follicular cell hypertrophy in animals receiving highest dose. Absolute and relative kidney weights were increased in females of all treatment groups and in males of the mid dose group. This was accompanied by dose-related proximal tubular hypertrophy in animals in the mid and high dose groups. Forestomach effects included hyperkeratosis and squamous cell hypertrophy. These effects are likely due to corrosivity of the chemical. A NOAEL of 100 mg/kg bw/day was reported based on the liver and kidney effects observed at 175 mg/kg bw/day (REACHd).

In a GLP compliant combined repeated dose toxicity study with the reproductive/developmental toxicity screening test conducted in accordance with OECD TG 422, Wistar rats (12/sex/dose) were administered dibutyl maleate by gavage once daily at 30, 95 and 300 mg/kg bw/day for a total of 40 days (males) and up to 50 days (females). Clinical signs of toxicity included unspecific signs of “reduced well-being” in the highest dose group. Liver and kidney weights were increased in animals receiving the highest dose. At this dose, males had a higher incidence of dermal hyperaemia (an excess of blood vessels supplying the area), lower body weights, higher albumin, total protein and bilirubin; and decreased mean corpuscular haemoglobin and renal tubular lesions including dilation, epithelial basophilia, and epithelial proliferation and karyomegaly (cells with an enlarged nucleus). The NOAEL for systemic toxicity was 95 mg/kg bw/day based on kidney and liver effects at 300 mg/kg bw/day (REACHa).

In a GLP compliant reproduction/developmental toxicity screening study conducted in accordance with OECD TG 421, Wistar rats (12/sex/group) were administered dimethyl maleate by gavage at 50, 200 and 400 mg/kg bw/day for a minimum of 28 days (males) and up to 54 days (females). Mortalities occurred at two highest doses (1 male from each group). One male and one female were euthanised for ethical reasons. Clinical signs of toxicity included increased salivation, ruffled fur and increased activity at the 2 highest doses. There were no effects on the mean absolute or relative organ weights. The animals receiving the highest dose had local irritation in the stomach. A NOAEL of 200 mg/kg bw/day was reported based on clinical signs of toxicity and stomach irritation at the highest dose (REACHc).

In a GLP compliant range-finding study, Wistar rats (3/sex/dose) were administered butyl hydrogen maleate by gavage once daily at 30, 100 and 300 (reduced to 225 mg/kg bw/day on day 5) mg/kg bw/day for 14 days. Treatment related effects in the animals dosed at high and mid levels were reported. One male from the high dose group was euthanised on day 5 because of excessive body weight levels and respiratory effects. The high dose level was subsequently reduced to 225 mg/kg bw/day. Surviving animals in this group had reduced body weight development and dietary intake, increased water consumption, increased salivation, noisy and laboured respiration and a decreased respiratory rate. Animals dosed with 100 mg/kg bw/day had less severe effects compared to the high dose group. A suitable maximum dose for future toxicity studies was considered to be 175 mg/kg bw/day (REACHd).

Dermal

In a short term repeated dose toxicity study conducted similarly to OECD TG 410, dimethyl maleate was applied dermally in olive oil to the shaved backs of Wistar rats (5/sex/group) at 60, 170 and 500 mg/kg bw under occlusive conditions for 6 hours/day, 5 days/week for a total of 20 applications. No treatment related mortality or systemic clinical symptoms were reported. Dose related local effects in the form of irritation were observed. The effects ranged from slight erythema and scaling at the lower doses to severe necrosis in the highest dose group. Food consumption and body weight gain were significantly reduced in male rats in the mid and high dose groups. The main effects of the clinical chemistry analyses were a 35% depletion of oxidised hepatic glutathione and a corresponding 37% decrease in the total hepatic glutathione level in the high dose group. Some variations in the haematological and clinico-chemical parameters were also observed in the high dose group animals. Absolute and relative organ weights of liver, kidneys, heart, brain, and adrenal glands were not significantly affected by the treatment. The histopathological examination did not reveal any treatment-related changes in the liver and kidney. The NOAEL for local effects was 170 mg/kg bw/day based on severe local irritation and necrosis at highest dose. The NOAEL for systemic effects is difficult to determine since the changes in clinical chemistry parameters may be secondary to the severe irritation and necrosis in observed in the highest dose group. (REACHc).

Inhalation

No data are available for the chemicals in this group.

Genotoxicity

Based on the available data for chemicals in this group, and data for maleic acid and maleic anhydride (NICNAS), this group of chemicals is not expected to be genotoxic. In vitro data available for 4 chemicals in this group were mostly negative and in vivo data for dibutyl maleate was also negative. Genotoxicity studies for maleic acid and maleic anhydride were mostly negative.

In vitro

Negative results were reported for bacterial reverse mutation and mammalian cell gene mutation assays conducted on maleic acid (CIR, 2007; OECD SIDS, 2004; REACHe). However, positive results were found in a DNA synthesis inhibition test (CIR, 2007).

Mostly negative results were reported in bacterial reverse mutation, chromosome aberration and mammalian cell gene mutation assays conducted on the chemicals in this group.

Negative results were reported in the following bacterial reverse mutation assays:

- In a GLP compliant assay, *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537 and *Escherichia coli* WP2uvrA were exposed to dibutyl maleate at concentrations up to 5,000 µg/plate with and without metabolic activation (REACHa).
- In a GLP compliant assay, *S. typhimurium* TA 97a, TA 98 TA 100 and TA 1535 were exposed to dibutyl maleate at concentrations up to 500 g/plate with and without metabolic activation (OECD SIDS, 2002).

- *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538 were exposed to dibutyl maleate at concentrations up to 5,000 ug/plate/plate with and without metabolic activation (REACHs).
- *S. typhimurium* TA 97, 98, TA 100, TA 102 were exposed to dibutyl maleate in a non-guideline study at concentrations from 100 to 1,000 µg/plate with and without metabolic activation (REACHa).
- In a GLP compliant assay, *S. typhimurium* TA 97a, TA 98, TA 100, TA 102 and TA 1535 were exposed to diethyl maleate at concentrations up to 5,000 µg/plate with and without metabolic activation (REACHb).
- In a GLP compliant assay, *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and 1538 were exposed to dimethyl maleate at concentrations up to 5,000 µg/plate with and without metabolic activation (REACHc).
- In a GLP compliant assay, *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537, and *Escherichia coli* WP2uvrA were exposed to butyl hydrogen maleate at concentrations up to 5,000 µg/plate with and without metabolic activation (REACHd).

Mixed results were reported in the following GLP compliant in vitro mammalian chromosome aberration assays (OECD TG 473):

- positive results when Chinese hamster ovary (CHO) cells were treated with dibutyl maleate at concentrations ranging from 5,000 µg/mL with and without metabolic activation (REACHa)
- negative results when human lymphocytes were treated with butyl hydrogen maleate at concentrations up to 1600 µg/mL with and without metabolic activation (REACHd).

Negative results were reported in GLP compliant mammalian gene mutation assay (OECD TG 476) in the thymidine kinase (TK) locus in mouse lymphoma cells L5178Y cells treated with:

- dibutyl maleate at concentrations ranging from 9.75 to 156 µg/mL with and without metabolic activation (REACHa)
- butyl hydrogen maleate in two independent experiments at concentrations ranging from 6.72-860 and 1.69-432 µg/mL with and without metabolic activation (REACHd).

Positive results were found in 2 in vitro assays using diethyl maleate but limited information was reported. The chemical was reported to cause mutations in the TK locus of mouse lymphoma L5178Y cells. However, the concentration required for a doubling of mutation resulted in 70% growth reduction. Positive results were reported in an aneuploidy test using V79 Chinese hamster lung cells at 8.7×10^{-6} M but not at 5.2×10^{-6} M. EFSA commented that aneuploidy is generally considered as a threshold phenomenon. No further details were available for either study. (EFSA, 2012).

In vivo

Negative results were reported in a chromosomal aberration test on maleic anhydride (NICNAS).

In a GLP compliant mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474, NMRI mice (5/sex/group) were administered dibutyl maleate by gavage at 2000 mg/kg bw. Animals were sacrificed at 24, 48 and 72 hours. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated

groups, indicating a lack of clastogenicity, but a slight clastogenic effect could not be excluded (OECD SIDS, 2002, REACHa).

In a non-guideline micronucleus assay, a single dose of 888 mg/kg bw dibutyl maleate (60% of the LD50) was administered to 30 male C3H mice by intraperitoneal injection. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow tissue, indicating that the chemical does not induce chromosomal aberrations in this test system (REACHa).

Carcinogenicity

No data are available for the chemicals. The chemicals in this group are not expected to be genotoxic carcinogens (see **Genotoxicity** section). Based on the read-across information from the analogues (maleic acid and maleic anhydride) (REACHe), the chemicals are not expected to have carcinogenic potential.

Reproductive and development toxicity

Based on the data for dimethyl, dibutyl maleate, butyl hydrogen maleate and the read-across information from maleic anhydride (NICNAS), the chemicals are not expected to cause specific adverse effects on fertility, sexual function or development following oral exposure.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422 (see **Repeat dose toxicity**) Wistar rats 12/sex/dose were administered dibutyl maleate by gavage once daily at 30, 95, and 300 mg/kg bw/day, from 14 days before mating for a total of 41 days (males) or from 14 days before mating to day 4 of lactation (females), during the premating, mating, gestation and lactation periods. One female receiving the highest dose lost a whole litter due to lack of nursing behaviour. This female also had multiple lesions on the heart, kidney and liver and; therefore, the outcomes for this animal are not considered to be specific reproductive toxicity. Pup mortality at birth was significantly increased in both mid and high dose groups. However, all but one pup loss in the highest dose group was attributed to the severely affected female. Therefore, the significance and dose-response relationship for pup mortality is difficult to determine. No information on number of pup deaths at the middle dose is available. No other treatment-related adverse effects were observed including effects on, mating index, gestation period, male and female fertility indexes, number of implantations and gestation length. The maternal observed adverse effect level (NOAEL) was 95 mg/kg bw/day based on significant adverse effects on liver and kidney observed at 300 mg/kg bw/day (REACHa; OECD SIAR, 2002).

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422 (see **Repeat dose toxicity**), Wistar rats 12/sex/dose were administered butyl hydrogen maleate by gavage once daily at 30, 100, and 175 mg/kg bw/day from 14 days before mating for a total of 43 days (males) or 14 days before mating to day 5 of lactation (females), during the premating, mating, gestation and lactation periods. The reported NOAEL for systemic toxicity was 100 mg/kg bw/day based on kidney effects at the highest dose. There were no treatment-related effects on the reproductive parameters investigated; therefore, the NOAEL for reproductive toxicity was considered to be 175 mg/kg bw/day (REACHd).

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422 (see **Repeat dose toxicity**) Wistar rats 12/sex/dose were administered dimethyl maleate by gavage once daily at 50, 200, 400 or 800 mg/kg bw/day from 14 days before mating for a total of 28 days (males) or from 14 days before mating to day 3 of lactation (females), during the premating, mating, gestation and lactation periods. The highest dose group (800 mg/kg bw/day) was removed from the study due to marked systemic effects. There was a significant increase in postnatal loss, reduced birth weights and reduced pup weights at day 4 postpartum in the 400 mg/kg bw/day dose group. There was also evidence of systemic toxicity in both males and female in this dose group. There were no treatment related effects on the reproductive parameters or organs investigated at 200 mg/kg bw. Therefore, the NOAEL for maternal and reproductive toxicity is 200 mg/kg bw/day (REACHc).

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