Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Maleic acid

Evaluation statement

14 January 2022

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AICIS Evaluation Statement

Subject of the evaluation

Maleic acid

Chemical in this evaluation

Name	CAS Registry Number
2-Butenedioic acid, (Z)-	110-16-7

Reason for the Evaluation

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

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory).This evaluation is a human health risk assessment for all identified industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

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

Based on international information, the chemical is used in a wide range of industrial applications, including in cosmetic products (as a pH adjuster and fragrance ingredient), in domestic products (air freshener products) and as an intermediate in chemical manufacturing.

Human health

Summary of health hazards

The critical health effects for risk characterisation include:

- systemic acute effects from oral exposure
- local effects (skin and eye irritation, respiratory tract irritation and skin sensitisation)
- systemic effects following repeated oral exposure.

Toxicology information for maleic acid is limited. Maleic anhydride is rapidly hydrolysed to maleic acid under aqueous conditions. Therefore the available data for maleic anhydride (CAS No. 108-31-6) are used to support to support the conclusions for systemic effects of maleic acid.

Based on the available toxicokinetic data, the chemical is readily absorbed and metabolised by the oral route, with oral bioavailability ranges of 30 to 40% in rats (Wu et al. 2016). Dermal absorption will largely depend on the chemical speciation of maleic acid in different vehicles. The chemical was reported to have linear pharmacokinetics when intravenously administered to rats, with a greater distribution to the kidney than the blood (Hou et al. 2016).

Maleic acid has moderate acute oral toxicity, with the lowest median lethal dose (LD50) value available being 708 mg/kg bw in rats. There was insufficient information to determine toxicity of the chemical via dermal and inhalation exposures.

The chemical is irritating to skin and eyes. Although a test guideline in vitro study (OECD TG 435) determined the chemical to be corrosive, animal and human data did not support this conclusion. Low concentrations of the chemical is irritating to the eyes of rabbits.

The chemical is classified as respiratory irritant. While there are no specific data to support or amend this classification, it is known that the chemical is a strong acid, with severe irritation effects to skin and eyes. The chemical dust would be expected to cause local irritation in the upper airways. Therefore, the chemical is considered to have respiratory tract irritation potential.

Based on the overall evidence, the chemical is a skin sensitiser; however, potency may vary depending on the amount of free acid available in solution. Positive results were reported in 3 local lymph node assays (LLNA). However, there was a difference in the potency of the chemical, which maybe due to the dissociation of the chemical in different vehicles. A negative result was reported in a guinea pig maximisation test (GPMT) when the chemical was used in Vaseline, and positive result was reported in another GPMT when the chemical was dissolved in saline solution. Limited human studies reported negative results when the chemical was tested at 0.3% in distilled water.

Following repeated exposure, maleic acid is expected to be toxic to the kidneys (target organ). Oral repeated dose toxicity studies in Sprague Dawley (SD) rats suggest that the chemical can induce renal changes at doses ≥100 mg/kg bw/day, including adverse effects at higher doses. The effects are not severe enough to warrant hazard classification.

There is currently no evidence that maleic acid has carcinogenic, mutagenic or reproductive toxicity potential. Based on the combined information from in vitro genotoxicity tests and available in vivo data for maleic anhydride, the chemical is not considered to be genotoxic. Carcinogenicity data from a chronic rat study did not indicate potential for the chemical to induce tumours. There are no reproductive toxicity data available for the chemical. However, negative results were reported for maleic anhydride in reproductive and developmental toxicity studies.

Health hazard classification

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for hazard classes relevant for work health and safety as follows.

This does not consider classification of physical hazards and environmental hazards. This is the current classification listed in the HCIS (Hazardous Chemical Information System) (SWA).

Health Hazards	Hazard Category	Hazard Statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Eye irritation	Eye Irrit. 2	H319: Causes serious eye irritation
Specific target organ toxicity (single exposure)	STOT Single Exp. 3	H335: May cause respiratory irritation
Skin irritation	Skin Irrit. 2	H315: Causes skin irritation
Skin sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction

Summary of health risk

Public

Based on the available use information, the public may be exposed to the chemical by:

- direct skin contact when using cosmetic products
- incidental skin and eye contact when using cosmetic or domestic products
- inhaling aerosols/vapours when using household products containing the chemical.

The available use data suggests that the chemical is mainly used as a buffering agent in cosmetic products. While the chemical may also be used as a fragrance it is not listed on the IFRA transparency list, indicating that its use as a fragrance is not widespread. The use of the chemical as buffering agent is not expected to expose the public to high concentrations of the free acid. The Cosmetic Ingredient Review (CIR) Expert Panel concluded that when maleic acid is used as a pH adjustor most of the acid would be neutralised into various maleate salts (CIR 2007), which are expected to be less potent skin sensitisers and irritants (AICIS).

At the expected low concentration of the chemical in cosmetic products; sensitisation, irritation and systemic effects are not expected to be a concern.

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

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 the chemical 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. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical systemic long-term, systemic acute and local health effects, the chemical could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risk to workers (refer to **Recommendation** section).

Conclusions

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

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

Recommendations

Workers

Information on managing identified risks

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 under the Model Work Health and Safety Regulations.

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 may need to be supplemented with:

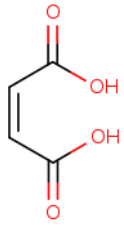
- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

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

Supporting Information

Chemical identity

Chemical name	2-Butenedioic acid, (Z)-
CAS No.	110-16-7
Synonyms	maleic acid
	1,2-ethylenedicarboxylic acid, (Z)
	cis-butenedioic acid
Structural Formula	
Molecular Formula	C4H4O4
Molecular Weight (g/mol)	116
SMILES	OC(=O)\C=C/C(=O)O
Chemical Description	cis unsaturated dicarboxylic acid

Relevant physical and chemical properties

Physical Form	Odourless white powder
Melting Point	138−139°C (crystallized from water)
	130−130.5°C (crystallized from alcohol)
	144°C (in air)
Boiling Point	ca 138°C
Vapour Pressure	4.8×10^{-3} Pa at 25°C
Water Solubility	407 g/L at 20°C
pKa	K1: 1.14×10^{-2} (pKa = 1.94) at 25°C
	K2: 5.95×10^{-7} (pKa = 6.22) at 25°C

log K_{ow}	-2.61
Particle size distribution (median particle size L50)	356 µm

The chemical is a dicarboxylic acid with a low pKa1, indicating a strong acid. It has a relatively low molecular weight and negative partition coefficient, indicating a highly hydrophilic chemical. Vapour pressure is low. Maleic acid is reported to decompose above the boiling point, and possibly isomerise into the trans isomer fumaric acid (CAS 110-17-8) (NLM; OECD 2004).

Introduction and use

Australia

No relevant information is available on the introduction and use of this chemical in Australia.

International

The following international uses have been identified through the:

- galleria Chemica database (Chemwatch)
- US National Library of Medicine's Pubchem database (NCBI)
- European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers
- Substances and Preparations in Nordic countries (SPIN) database
- European Cosmetic Ingredient Database (CosIng)
- the Cosmetic Ingredient Review (CIR) report on maleic acid (CIR, 2007)
- OECD Screening Information Dataset (SIDS) Initial Assessment Report (SIAR) on maleic anhydride and maleic acid (OECD 2004).

The chemical has reported cosmetic use including as a fragrance ingredient and pH adjuster.

The chemical was identified in hair products and shaving creams in 2002, and was reported at a concentration of 0.004% in bath products in a 2004 survey (CIR 2007).

The chemical is not listed on the International Fragrance Association (IFRA) transparency list (IFRA 2017). The IFRA Transparency List is an ordered register of all fragrance ingredients used in consumer goods by the fragrance industry's customers worldwide. It represents a snapshot of all the ingredients used in active formulas at the time of publication.

The chemical has reported domestic use in household cleaning products such as air freshener products.

The chemical has reported commercial uses including in:

- cleaning/washing agents
- adhesive and binding products
- textile dyeing and finishing products
- food contact material.

The chemical has reported site limited use as an intermediate in producing other chemicals such as artificial resins, tetrahydrofuran, fumaric acid and 1,4-butanediol (CIR 2007; EPA 2006; OECD 2004).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

Workers

The chemical is classified as hazardous with the following risk phrases for human health in the Hazardous Chemical Information System (HCIS) (SWA):

- Acute toxicity – Category 4; H302 (Harmful if swallowed)
- Eye irritation – Category 2; H319 (Causes serious eye irritation)
- Specific target organ toxicity (single exposure) – Category 3; H335 (May cause respiratory irritation)
- Skin irritation – Category 2; H315 (Causes skin irritation)
- Skin sensitisation – Category 1; H317 (May cause an allergic skin reaction).

No exposure standards are available for this chemical in Australia.

International regulatory status

Exposure standards

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

- TEEL-1 = 2.3 mg/m^3, concentration of the chemical 'above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, these effects are not disabling, are transient and reversible upon cessation of exposure.' (US DOE 2018)
- TEEL-2 = 23 mg/m^3, concentration of the chemical 'above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience irreversible or other serious, long-lasting, adverse health effects or an impaired ability to escape.' (US DOE 2018)
- TEEL-3 = 140 mg/m^3, concentration of the chemical 'above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience life-threatening adverse health effects or death.' (US DOE 2018)

United States of America

The CIR Expert Panel concluded that maleic acid is safe for use in cosmetic formulations as a pH adjustor as described in the safety assessment (CIR 2007).

Health hazard information

Toxicokinetics

In a pharmacokinetic study using SD rats, the chemical was orally administered to groups of male and female rats. Results showed linear pharmacokinetics, with the chemical being readily absorbed and metabolised. The half-life of maleic acid in serum was 17.58 hours and 9.84 hours for low dosed male and female rats, and 8.24 hours and 4.17 hours for high dosed male and female rats, respectively. Oral bioavailability ranged from 30.8 to 41.0% for males and 32.2 to 39.1% for females (Wu et al. 2016).

Based on its highly hydrophilic nature, dermal absorption is expected to be limited for the chemical itself. Based on its particle size distribution, the chemical is not expected to be easily absorbed via inhalation, as it would be limited to the upper airways. The structurally similar chemical acrylic acid (CAS No. 79-10-7) is reported to have dermal absorption levels between 10% and 25% in rodents (NIOSH 2017).

In another study, the pharmacokinetics of the chemical in kidney and blood was investigated in groups of 5 rats treated with intravenous doses of 10 or 30 mg/kg bw of the chemical (Hou et al., 2016). The total body clearance (CL) of maleic acid at 10 and 30 mg/kg bw in the blood were 27.4 and 25.3 mL/min/kg, respectively. In the kidney, the CL of maleic acid at 10 and 30 mg/kg bw were 5.45 and 5.34 mL/min/kg, respectively. Results showed higher volume of distribution (Vd) in the blood than in the kidney. The C_{max} in the kidney was around 4 times higher than that in the blood, and the AUC (area under curve) in the kidney was 5 times higher than that in the blood, indicating a relative accumulation of the chemical in the kidney (Hou et al. 2016).

In a study described by the CIR (CIR 2007), radiolabelled chemical was injected to a dog and a human volunteer in order to determine if the chemical was metabolised into CO_2. In both the dog and the human volunteer, arterial CO_2 labelled with ^{14}C increased over time after injection (no further details available). The study concluded that in both cases, there were enzymes capable of metabolising the chemical into CO_2 (CIR 2007).

Acute toxicity

Oral

Based on the available data, the chemical has low to moderate acute oral toxicity, supporting the current hazard classification.

The following median lethal dose (LD50) values are available:

- 2870 mg/kg bw in rats, based on a study following OECD TG 401 (REACH)
- 708 mg/kg bw in rats, based on the results from an unpublished report (OECD 2004).

Similar oral LD50 values are reported for maleic anhydride (1030–1090 mg/kg bw) in rats (OECD 2004; REACH; NICNAS 2015).

Dermal

Limited data are available for the chemical.

A dermal LD50 of 1560 mg/kg bw in rabbits was reported based on results from an unpublished non-guideline study (OECD 2004; REACH).

Inhalation

No data are available for the chemical.

Corrosion/Irritation

Skin Irritation

Based on the available data from in vitro, animal and human studies the chemical is irritating to the skin, supporting the current hazard classification. Although the in vitro study determined the chemical to be corrosive consistent with the low pKa value, animal studies did not support this observation.

In an in vitro skin corrosion study, conducted in accordance with OECD TG 435 (in vitro membrane barrier test method for skin corrosion), 500 mg of maleic acid was applied to the membrane barrier in triplicate. The mean time to break through the membrane and subsequently activate the underlying chemical detection system (CDS) was 25 minutes. The positive control for this test (sodium hydroxide) had a mean penetration time of 22 minutes and the negative control had a penetration time of 95 minutes. Based on the criteria of the assay, the chemical was determined to be corrosive to the skin (REACH).

Application of 500 mg maleic acid to the skin of rabbits and guinea pigs for 24 hours resulted in slight irritation. No further details were provided (OECD 2004).

Eye Irritation

Based on the available data from animal studies, the chemical is irritating to the eyes at low concentrations, supporting the current hazard classification.

In an eye irritation study, the chemical was applied at 1% or 5% into the conjunctival sac of the right eye of rabbits (n = 2/concentration) for two minutes, then allowed to drain. At 1%, the chemical caused cloudiness of the cornea, hyperaemia of the conjunctivae and oedema of the nictating membrane within a few minutes. The effects were reversible within 24 hours. At 5%, the chemical produced qualitatively similar, but more intense effects, including iris and cornea irritation; effects were reversible within 6 or 7 days (REACH).

The chemical was reported to cause moderate to severe irritation to the eyes of rabbits when applied at 1% (NCBI). No further details on the study were provided.

Respiratory irritation

No data are available for the chemical.

Observation in humans

Based on the available human data, the chemical is a skin irritant.

In a skin irritation study in humans, the chemical at 20% in propylene glycol was applied to the forearm and labia majora of 21 female volunteers for 24 hours. Results varied from 'minimal erythema to marked erythema with marked vesiculation', but no further details were reported. A total of 76% of the volunteers had vulvar skin irritation and 62% had forearm skin irritation (CIR).

In a study in humans, the chemical at 20% was applied daily to the forearm skin of 50 volunteers for 6 weeks. Acute vesicular dermatitis was observed in 17 volunteers, between week 4 and 6. Those 17 volunteers were excluded from the study. At the end of week 6, the chemical at 20% was applied in a 4 hour closed patch test on both the untreated and treated forearm of all remaining volunteers. Apart from five volunteers who showed no response, the study reported that the remaining volunteers exhibited a range of inflammation or hyperirritable skin effects (CIR).

In a study in 12 human volunteers, the chemical at 5% in aqueous solution was applied three times to the intact skin of the volunteers. The duration of application was 24 hours per application. The study indicated that the chemical was irritating to the skin. The mean irritation score was 0.86 (maximum 2.5). Necrotic responses were reported but no further details were provided (REACH).

Sensitisation

Skin Sensitisation

The chemical is a skin sensitiser based on the results seen in local lymph node assays (LLNA), guinea pig maximisation tests (GPMT) and a direct peptide reactivity assay (DPRA).

Local lymph node assays (LLNA)

In a LLNA conducted in accordance with OECD TG 429, female CBA mice (n = 5/group) received topical applications of the chemical at 10, 25 and 50% in DMSO (dimethylsulfoxide) for 3 days. The reported stimulation indices (SI) were 6.7, 16.1 and 16.1 respectively. The reported concentration producing a three fold increase in lymphocyte proliferation (EC3) is therefore <10%, indicating moderate sensitisation potential (Kreiling et al. 2008).

In another LLNA conducted in accordance with OECD TG 429, female CBA mice (n = 5/group) received topical applications of the chemical at 1, 2.5 and 5% in dimethylformamide for 3 days. The reported stimulation indices (SI) were 11.2, 22 and 31.5, respectively. The EC3 is therefore expected to be <1%, indicating strong sensitisation potential (REACH).

In a modified LLNA with an elicitation phase (LLNA:DAE), female CBA mice (n = 1/group) were treated with concentrations of 0, 5, 10, 25 or 50% of the chemical in DMSO. The chemical was applied to the dorsum of the right ear on days 1, 2 and 3, then applied to the dorsum of both ears on day 10. A clear dose dependent increase in lymph node weight of the right ear was reported, and excessive skin irritation was observed with 5 and 10% of the chemical.

Following this preliminary study, a group of 5 mice was then treated with the chemical at 50% in DMSO, applied to the dorsum of the right ear on days 1, 2 and 3, then applied to the

dorsum of both ears on day 10. Based on the degree of increase in lymph node weight of the left ear, maleic acid was reported to be positive for eliciting skin sensitisation. The study authors (Yamashita et al., 2015) indicated that maleic acid only showed weak skin sensitisation potential, in contrast with previous results (Kreiling et al. 2008).

Guinea pig maximisation tests (GPMT)

Negative results were reported in a skin sensitisation study conducted in accordance with OECD TG 406 (guinea pig maximisation test (GPMT) (Kreiling et al., 2008). A group of 10 female guinea pigs were treated with the chemical at 0.5% in isotonic saline via intradermal injection on day 0 and the chemical at 25% in Vaseline via topical administration on day 7. The animals were then topically challenged with the chemical at 25% in Vaseline for 24 hours on day 20, followed by a rechallenge on day 28. Only 1/10 animals showed a grade 1 skin reaction after challenge, observed 24 and 48 hours after the patch was removed. Following rechallenge, the observed skin reaction was not reproducible, so the animal was not considered sensitised overall (Kreiling et al. 2008).

Ambiguous results were observed in another GPMT following OECD TG 406. For induction, female Dunkin Hartley guinea pigs (n = 10) were treated with an intradermal dose of 1% of the chemical in saline on day 0, then with a topical dose of the chemical at 35% in deionised water on day 8. The animals were then topically challenged with the chemical at 25% in deionised water on day 22. All tested animals (10/10), including in the control group (5/5), showed severe erythema and/or oedema, considered as mainly a skin irritation response. A second challenge was conducted using a lower concentration (1% in deionised water) on day 28. Results showed that 24 and 48 hours after the second challenge exposure, 3/10 treated animals had severe erythema and/or oedema. No skin reactions were observed in the control animals. Therefore, 30% of treated guinea pigs were considered to be sensitised following exposure to the chemical. However, the concentrations used for the study may have been inappropriate, as it is reported that 1% caused severe skin reactions in 3/3 guinea pigs tested during a preliminary study (OECD 2004; REACH).

Direct Peptide Reactivity Assay (DPRA)

A positive result was reported for the chemical when tested in a direct peptide reactivity assay (DPRA) similar to OECD TG 442C, using defined ratios of peptide to test item (1:10 cysteine peptide, 1:50 lysine peptide) in water. Mean cysteine and lysine depletion by the chemical was 29.8%, indicating peptide binding. The chemical was found to have peptide binding capacity ‘resembling that of true skin sensitisers’ with average peptide reactivity >6.376% (Yamashita et al. 2015).

Observation in humans

In a human repeat insult patch test (HRIPT), human subjects (n = 105) were treated with occlusive patch containing 0.5 mL of 0.3% v/v maleic acid in distilled water, 3 times/week for 3 weeks. No positive responses were observed in any of the subjects and the chemical was considered to be non-sensitising in this study (REACH).

Repeat dose toxicity

Oral

Based on the combined available data for maleic acid and maleic anhydride, the chemical is potentially harmful following repeated oral exposure. Effects on the kidneys were reported in

several rat studies at doses >100 mg/kg bw/day; however, the effects seen were severe enough to warrant hazard classification for maleic acid.

In a non-guideline two year feeding study (OECD SIDS; REACH), groups of 12 male Osborne Mendel rats were given food containing 0, 0.5, 1 or 1.5% of the chemical (equivalent to 0, 250, 500 and 750 mg/kg bw/day, respectively). At high and mid doses, significant decreases in body weight and body weight gain were reported (REACH). After 18 months of treatment, there were increased mortality rates at high and mid doses. After 24 months, mortality rates were 10/12 at low and mid doses and 12/12 at the high dose, compared with 6/12 in controls. Histopathological changes were reported in liver, testes and kidneys. In the kidneys, enlarged and irregularly shaped epithelial cells in small to moderate numbers of renal tubules, generally the proximal convoluted tubules, were observed in four rats at high dose and in three rats at mid dose. Liver and testes atrophy were observed at high dose but no further details were provided (REACH). A no observed adverse effect level (NOAEL) could not be established in this study. Based on the results, a lowest observed adverse effect level (LOAEL) of 250 mg/kg bw/day could be determined.

In a non-guideline subchronic oral toxicity study, SD rats (n = 15/sex/dose) were administered maleic anhydride in the diet at doses of 0, 100, 250 or 600 mg/kg bw/day for 90 days. At 600 mg/kg/day, there was slight proteinuria in both sexes, increased relative liver weight in males and increased relative/absolute kidney weights in both sexes. At 250 mg/kg/day, there were increased relative/absolute kidney weights in males. Grossly observed kidney changes were seen in males fed maleic anhydride 100, 250, and 600 mg/kg/day. Changes were characterised by increased size, pale discolouration, and evidence of dilated tubules in the cortex. These consisted of diffuse tubular dilatation, hypertrophy, and degeneration and regeneration of the tubular cells in the cortical portion of the nephron. Kidney changes increased in severity and in number in a dose dependent manner, as they were reported in 5/15 low dosed male rats, 10/15 mid dosed rats and 15/15 high dosed rats. Microscopically, the kidneys showed varying degrees of nephrosis, being most severe in the high dose group. Similar changes were observed in the kidneys of females, but were generally limited to the high dose group and were much less severe. Based on the renal effects, LOAEL values of 250 mg/kg bw/day for female rats and 100 mg/kg bw/day for male rats were determined in this study (ECHA 2016; OECD 2004).

In a subchronic oral toxicity study, SD rats (n = 50/sex/dose) were administered maleic anhydride in the diet at 0, 250 or 600 mg/kg bw/day for 90 or 183 days. A LOAEL of 250 mg/kg bw/day was determined based on the significant changes on liver, kidney and heart weights and renal changes (generalised tubule dilatation and hypertrophy, degenerative tubules and tubules showing mitotic activity and marked decrease in the amount of functional tissue). Effects were observed in a dose dependent manner (ECHA 2016).

In a two generation reproductive toxicity study, SD rats were administered oral doses of maleic anhydride at 0, 20, 55 or 150 mg/kg bw/day during pre-mating, and throughout mating, gestation and lactation period. A LOAEL of 20 mg/kg bw/day was determined for systemic toxicity based on kidney changes in all dose groups of the F0 parents (hydronephrosis/dilated pelvis, kidneys with a mottled appearance or irregular surface and calculi in the urinary bladder). Renal necrosis was observed at the high dose in 60% of the male and 15% of the female F0 rats. In the F1 generation, kidney weights were significantly increased in females from the low and mid dose groups, but there were no microscopic changes (ECHA 2016; OECD SIDS).

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Genotoxicity

In vitro

The chemical was found negative in a bacterial reverse mutation assay in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 at concentrations up to 7500 µg/plate (CIR 2007; OECD 2004; REACH).

The chemical was found negative in a mammalian cell gene mutation assay following OECD TG 476 at concentrations up 1200 µg/mL. No relevant and reproducible increases in mutations were observed in the main experiments up to the maximum concentration. No precipitation of the test item was observed up to the maximal concentration in all experiments. Cytotoxic effects were reported at 900 µg/mL and above in one of the experiments without metabolic activation following 24 hours of exposure (REACH).

In a DNA synthesis inhibition test in human fibroblasts, the chemical showed a positive pattern in the DNA synthesis inhibition test: a decreased rate of DNA synthesis was observed after 90 min, followed by recovery after 150 min (CIR 2007).

In vivo

No data are available for the chemical.

Maleic anhydride was negative in a chromosomal aberration test using SD rats exposed to 0, 0.25 or 25 ppm for 6 hours. No signs of toxicity in the bone marrow cells were observed. There were no treatment related effects on the frequency of chromosomal aberrations. A statistically significant increase in chromosome number was observed in the low dose animals at 6 hours and in the high dose animals at 24 hours; these were not considered treatment related (OECD 2004).

Carcinogenicity

In a non-guideline two-year feeding study (OECD, 2004; REACH), groups of 12 male Osborne Mendel rats were given the chemical at 0, 0.5, 1 or 1.5% in the feed (equivalent to 0, 250, 500 and 750 mg/kg bw/day, respectively). At high and mid doses, significant decreases in body weight and body weight gain were reported (REACH). After 18 months of treatment, there were increased mortality rates at mid and high doses. After 24 months, mortality rates were 10/12 at low and mid doses and 12/12 at high doses, compared with 6/12 in controls. No treatment related increase in tumours were reported.

In a two year feeding study, groups of Fischer rats (n = 126/sex/dose) were given 0, 10, 32 or 100 mg/kg bw/day maleic anhydride in the diet. At 6 and 12 months, five animals of each group, and 20 rats per group at 18 months were euthanised for examination. Results showed marginal toxicity with small (<6%), but dose related, decrease in body weights of male rats at mid and high doses, compared with controls. At these doses, female rats also had reduced body weights, but the reductions were smaller and of shorter duration than those observed in males. Food consumption was slightly reduced during limited periods during the study for animals in the mid and high dose groups. There was a 100% incidence of cataracts in the animals examined at 18 months and at study termination, but this was not

considered treatment related. An unusually high incidence of uterine adenocarcinomas was reported in both the control group and one of the treated groups (23/86 and 20/82, respectively). This type of effect was reported as ‘not a common spontaneous lesion in this strain of rat’ (OECD, 2004; REACH), but no historical control data was provided and the occurrence in the control group indicated it was not related to treatment with maleic anhydride. Overall, there were no treatment related increases in tumour incidence.

Reproductive and development toxicity

No data are available for maleic acid.

In a two generation reproductive toxicity study, SD rats (n = 10 males/dose and 20 females/dose) were administered oral doses of maleic anhydride at 0, 20, 55 or 150 mg/kg bw/day during pre-mating (80 days minimum in F0 and F1 rats), and throughout mating, gestation and lactation period. In F0 and F1 animals, significant mortality occurred at high dose for both sexes (100% mortality rate in F1 female rats by week 42). Significant decreases in fertility were reported for some of the treated animals, but considered as not treatment related. No further details were provided. No adverse effects on litter size or pup survival were reported up to the highest dose in the F1 litters, or at 55 mg/kg/day in the F2 litters. Microscopic examination of tissues from pups in the F2 litters revealed no treatment related changes. A NOAEL of 55 mg/kg bw/day for reproductive toxicity was determined based on the absence of adverse effects on litter size and pup survival in the two generations (OECD 2004; REACH).

In a developmental toxicity study (Short et al., 1986), female CD rats (n = 25/dose) were given by gavage 0, 30, 90 or 140 mg/kg bw/day maleic anhydride in corn oil during days 6 to 15 of gestation. One adult female died in each treatment group. There were no statistically significant effects on body weight gains at any interval, although females at low dose failed to gain weight from gestation day 6-9. There was no effect on litter size, and no sign of post-implantation loss. There were slight decreases in foetal body weight observed in all treatment groups, and this was statistically significant in the low and high dose groups. However, this was not considered to be treatment related because values reported in control and all treated groups were slightly greater than the historical control values. Malformations were observed in one foetus (1/23 litters) from the control group, two foetuses (2/23 litters) from the low dose group and three foetuses (3/21 litters) from the high dose group. Each malformation was reported as a single occurrence. There were no differences in foetal variations between the control and treated groups. The NOAEL for both maternal and developmental toxicity was 140 mg/kg/day (OECD 2004).

Other

Nephrotoxicity

Two Japanese white rabbits receiving a single subcutaneous injection of 400 mg/kg bw of the chemical died within 24 hours. Necropsy showed pyonephrosis (pus accumulated in the renal pelvis) in both animals (CIR 2007).

Acute tubular necrosis was observed in 1/3 female and 3/3 male beagle dogs fed with a single dose of maleic acid, within 24 hours. The lowest dose of the chemical producing evidence of nephrotoxicity was 9 mg/kg bw of maleic acid (CIR 2007).

Intraperitoneal injection of the chemical in rats was shown to increase the excretion of phosphate, glucose and amino acids in urine, displaying similar effects as the human Fanconi syndrome (CIR 2007).

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