

MALEIC ANHYDRIDE

CAS number: 108-31-6

Synonyms: cis-Butenedioic anhydride, 2,5-Furandione, maleic acid anhydride, MA

Chemical formula: $C_4H_2O_3$

Structural formula: —

Workplace exposure standard (amended)

TWA: 0.0025 ppm (0.01 mg/m³)

STEL: —

Peak limitation: —

Notations: Sk, DSEN, RSEN

IDLH: —

Sampling and analysis: The recommended value is quantifiable through available sampling and analysis techniques. .

Recommendation and basis for workplace exposure standard

A TWA of 0.0025 ppm (0.01 mg/m³) is recommended to protect for irritant effects and minimise the potential for respiratory sensitisation in exposed workers.

Discussion and conclusions

Maleic anhydride (MA) is produced through oxidation of n-butane or vapour phase oxidation of benzene and used in the production of polyester resins used in coatings, epoxies, ink, pesticides, lubricant additives and pharmaceuticals.

The critical effect from exposure is potential respiratory sensitisation and irritation. The minimal concentration of 1 g/m³ is associated with conjunctival and upper respiratory tract irritation. A retrospective examination of a cohort of 506 workers from four factories reported sensitisation was not identified in workers with recent exposures at 0.0028 mg/m³ (arithmetic mean). Sensitisation occurred in workers with past exposures ranging from 0.005 to 0.054 mg/m³ (ACGIH, 2018). Irritation of the nose and eyes, nasal discharge, dyspnoea and sneezing observed in rats, hamsters and monkeys exposed at 1.1 mg/m³ (the lowest dose tested) for 6 months (ACGIH, 2018).

A TWA of 0.01 mg/m³ (0.0025 ppm) is recommended as derived by ACGIH (2018). This TWA is expected to be protective of irritation and respiratory sensitisation.

Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Classified as a skin sensitizer and respiratory sensitizer according to the GHS.

A skin notation is recommended based on evidence suggesting potential dermal absorption and adverse systemic effects in animals.

DRAFT

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	1991	TWA: 0.25 ppm (1 mg/m³)
ACGIH	2014	TLV-TWA: 0.0025 ppm (0.01 mg/m³) (inhalable fraction and vapour)
<p>TLV-TWA recommended for inhalable fraction and vapour to minimise potential for respiratory sensitisation based on human reports and positive animal responses.</p> <p>Summary of data:</p> <p>Sufficient data available to recommend both RSEN and DSEN notations causing asthma, haemolytic anaemia and urticaria.</p> <p>RSEN notation based on IgE antibodies detected in workers. DSEN based on animal studies with limited human evidence.</p> <p>Human data:</p> <ul style="list-style-type: none"> Reported minimal concentration associated with conjunctival and upper respiratory tract irritation was 1 mg/m³; likely threshold; 0.9 mg/m³ (0.22 ppm) without a discernible adverse effect; no further information Retrospective examination of a cohort of 506 workers from 4 factories: <ul style="list-style-type: none"> 2 factories had mean MA full-shift exposures of 1.8 and 2.8 µg/m³; past concentrations of up to 5.4 µg/m³; task specific exposures of 1.4–28.6 µg/m³; reported sample times of 13–83.5 min 3rd factory had past exposures of up to 54 µg/m³ affected workers from these factories were not recently sensitised by acid anhydrides; indicates past exposures carried higher risk than recent low exposures found 13% of former exposed workers developed respiratory symptoms compared to 3.6% of newer workers full shift exposures at ≥10 µg/m³ carries more risk of sensitisation than exposures at ≤10 µg/m³ Case study of 93 chemical workers (unknown concentrations): reported dyspnoea, rhinitis, conjunctivitis and phlegm production: <ul style="list-style-type: none"> 6 workers had positive IgE antibody response to MA-human serum albumin (HSA) MA-HSA specific IgE antibodies found to be still present in 2/3 workers no longer exposed Case studies confirm irritation of mucosa, eye pain, blurred vision and keratitis Case study in MA sensitised worker; cough, rhinitis, breathlessness, and wheezing, began within one month following exposure; symptoms then appeared within minutes of exposure; total and respirable dust concentrations during the 2 h process of 0.83 and 0.17 mg/m³ respectively Ceramic workers demonstrated contact sensitisation (2 workers) with allergic dermatitis response. <p>Animal data:</p> <ul style="list-style-type: none"> Nasal and eye irritation following inhalation at 1.1, 3.3 or 9.8 mg/m³ in multi-species study (rats, hamsters and Rhesus monkeys; 6 h/d 5 d/wk for 6 mo) Extremely irritating to rabbit eyes (0.1 g; undiluted) LD₅₀: 2.6 g/kg (albino NZ rabbits, dermal) 		



Source	Year set	Standard
<ul style="list-style-type: none"> Negative <i>S. typhimurium</i> strain results Negative chromosomal changes <i>in vivo</i> (rat bone marrow). 		
DFG	2018	MAK: 0.02 ppm (0.081 mg/m³)
<p>MAK value determined by critical effect on respiratory tract or eyes.</p> <p>Skin contact not expected to contribute significantly to systemic toxicity.</p> <p>Additional information:</p> <p>Animal data:</p> <ul style="list-style-type: none"> LOAEC inhalation: 0.27 ml/m³ (multi species, 6 mo) Not genotoxic <i>in vitro</i> or <i>in vivo</i>. 		
SCOEL	NA	NA
No report.		
OARS/AIHA	NA	NA
No report.		
HCOTN	2010	Not assigned
<p>Induction of allergic sensitisation considered critical adverse health effect for cyclic acid anhydride group.</p> <p>Recognises international range of exposure standards between 400–1,200 µg/m³ for maleic anhydride.</p> <p>Abstains from making recommendations for maleic anhydride due to lack of adequate data on allergic sensitisation and respiratory symptoms to derive an HBR-OEL.</p> <p>Additional information:</p> <ul style="list-style-type: none"> No data on uptake after inhalation or via other routes of exposure is known Human and animal specific IgE antibodies identified in blood pointing to allergic sensitisation Exposures after being sensitised may lead to urticaria, allergic rhinitis, conjunctivitis and allergic asthma Skin contact may lead to contact urticaria. 		

Secondary source reports relied upon

Source	Year	Additional information
NICNAS	✓ 2015	<ul style="list-style-type: none"> 2,5-furandione: Human health tier II assessment Moderate acute dermal toxicity in rats, warranting hazard classification Limited inhalation data available – animal testing indicates respiratory and eye irritation LC₅₀: inhalation >4.35 mg/L (mice, 1 h) Human case studies support RSEN classification.
NTP	* 2018	<ul style="list-style-type: none"> No further information.



Source	Year	Additional information
US EPA	✓ 1988	<ul style="list-style-type: none"> Chronic oral exposure assessment only NOAEL: 10 mg/kg/d (rats, oral).
ECHA	✓ 2019	<ul style="list-style-type: none"> Repeat inhalation dose toxicity (DNEL: 190 µg/m³) for workers Acute and short-term inhalation causes respiratory tract irritation (DNEL: 800 µg/m³) No local dermal effect threshold derived Dermal systemic effects for repeat dose: (DNEL 200 µg/kg/d) High eye exposure hazard.
OECD	✓ 2004	<ul style="list-style-type: none"> Low acute toxicity by oral and dermal routes Human data indicating asthma related to exposure has been questioned Properties indicating hazard for human health as skin and eye irritant with skin and possible respiratory sensitisation effects.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic? No

Is the chemical carcinogenic with a mutagenic mechanism of action? No

The chemical is not a non-threshold based genotoxic carcinogen.

Notations

Source	Notations
SWA	—
HCIS	Skin sensitisation – category 1, Respiratory sensitisation – category 1
NICNAS	NA
EU Annex	Skin sensitisation – category 1, Respiratory sensitisation – category 1
ECHA	NA
ACGIH	Carcinogenicity – A4, DSEN, RSEN
DFG	Sh (dermal sensitiser), Sa (respiratory sensitiser)
SCOEL	NA
HCOTN	—
IARC	NA
US NIOSH	NA

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations



Skin notation assessment

Calculation

Conclusion:

Adverse effects in human case study: **yes**
Dermal LD₅₀ ≤1000 mg/kg: **yes**
Dermal repeat-dose NOAEL ≤200 mg/kg:
Dermal LD₅₀/Inhalation LD₅₀ <10:
In vivo dermal absorption rate >10%:
Estimated dermal exposure at WES >10%:

a skin notation is warranted

IDLH

Is there a suitable IDLH value available? No

Additional information

Molecular weight:	98.06
Conversion factors at 25°C and 101.3 kPa:	1 ppm = Number mg/m ³ ; 1 mg/m ³ = Number ppm
This chemical is used as a pesticide:	<input checked="" type="checkbox"/>
This chemical is a biological product:	<input type="checkbox"/>
This chemical is a by-product of a process:	<input checked="" type="checkbox"/>
A biological exposure index has been recommended by these agencies:	<input type="checkbox"/> ACGIH <input type="checkbox"/> DFG <input type="checkbox"/> SCOEL

Workplace exposure standard history

Year	Standard
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References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [TLVs® and BEIs® Guidelines section](#) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2018) Maleic anhydride – MAK value documentation.

European Chemicals Agency Regulation (ECHA) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

Health Council of the Netherlands (HCOTN) (2010) Cyclic acid anhydrides. Health-based recommended occupational exposure limit. The Hague: Health Council of the Netherlands; publication no. 2010/02OSH.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2015) 2,5-Furandione: Human health tier II assessment – IMAP report.

National Toxicology Program (NTP) (2018) NTP-Testing status: Maleic anhydride. 10519-E.

Organisation for Economic Cooperation and Development (OECD) (2004) SIDS initial assessment profile – maleic anhydride and maleic acid.

Tenth Adaptation to Technical Progress Commission Regulation (EU) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).

US Environmental Protection Authority (US EPA) (1998) Integrated Risk Information System (IRIS) Chemical Assessment Summary – Maleic anhydride.