Maleic anhydride

MAK Value Documentation, supplement – Translation of the German version from 2018

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated maleic anhydride [108-31-6], considering all toxicological end points. Available publications and unpublished study reports are described in detail. Maleic anhydride is an irritant to the upper respiratory tract. A LOAEC of 0.27 ml/m^3 for nasal and ocular irritation was obtained from a 6-month inhalation study in rats, hamsters and monkeys. Since 2014 the Commission uses an empirical approach to set the maximum concentration at the workplace (MAK value) for substances with critical effects on the upper respiratory tract or the eyes. Based on this, the MAK value for maleic anhydride is set at 0.02 ml/m^3 (0.081 mg/m^3). Since the critical effect of maleic anhydride is local, Peak Limitation Category I with an excursion factor of 1 is confirmed and a momentary value of 0.05 ml/m^3 is set. Damage to the embryo or foetus is unlikely when the MAK value is not exceeded and maleic anhydride remains assigned to Pregnancy Risk Group C. Maleic anhydride is not genotoxic in vitro and in vivo. No increased tumour incidence was observed in a chronic feeding study in rats. Skin contact is not expected to contribute significantly to systemic toxicity. In humans, airway sensitization is observed. There are positive results of contact sensitization in mice and guinea pigs. Maleic anhydride continues to be designated with "Sah".
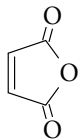
MAK value (2017)	**0.02 ml/m³ (ppm) ≙ 0.081 mg/m³**
Peak limitation (2017)	**Category I, excursion factor 1, momentary value 0.05 ml/m³**
Absorption through the skin	**–**
Sensitization (1991)	**Sah**
Carcinogenicity	**–**
Prenatal toxicity (1991)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	*cis*-butenedioic anhydride dihydro-2,5-dioxofuran furan-2,5-dione maleic acid anhydride
Chemical name (CAS)	2,5-furandione
CAS number	108-31-6
Structural formula	

Molecular formula	$C_4H_2O_3$
Molar mass	98.06 g/mol
Melting point	53–58 °C (ECHA 2015)
Boiling point	200.1 °C (ECHA 2015)
Vapour pressure at 22 °C	0.151 hPa (ECHA 2015)
log K_{OW}	−2.36 (ECHA 2015), substance hydrolyses
Solubility	400 g/l water (ECHA 2015), substance hydrolyses
1 ml/m³ (ppm) ≙ 4.069 mg/m³	**1 mg/m³ ≙ 0.246 ml/m³ (ppm)**

Documentation for maleic anhydride was published in 1991 (Henschler 1992), followed by supplements on airway sensitization in 1995 (Greim 1998) and on peak limitation in 2000 (Greim 2000 a, available in German only).

No new studies with repeated exposure are available.

Maleic anhydride is rapidly hydrolysed to maleic acid (see also Section 5.6.2; Monsanto Co 1983).

A large number of reviews of the toxicological action profile of maleic anhydride have been published, including a report of the ACGIH (2014 a), an evaluation of the Danish Environmental Protection Agency (2013), a report of the Health Council of the Netherlands (2010), documentation by the Nordic Expert Group (Keskinen 2004) and a review by OECD (2005).

Maleic anhydride is used in the production of polyester resin (Venables 1989).

A number of studies reported concentrations for maleic anhydride at the workplace.

In 2 plants, the individual levels of exposure to maleic anhydride during the shift ranged from 0.0004 to 0.0024 mg/m^3 with a 13-minute peak of 0.0172 mg/m^3. Another study reported short-term exposure to maleic anhydride at levels of 5.35 mg/m^3 (up to 22 mg/m^3) while transferring maleic anhydride powder from one container to another. A mean concentration of 0.1278 mg/m^3 with a peak value of 0.78 mg/m^3 was determined in another plant. No information was provided about the specific activities being performed as the determinations were carried out (OECD 2005). Maleic anhydride concentrations of 0.83 mg/m^3 for the inhalable particulate mass and 0.17 mg/m^3 for the respirable particulate mass were determined while filling a reactor in a polyester resin manufacturing plant (Lee et al. 1991).

In a cohort study carried out in 3 plants, the current mean exposure concentrations ranged from 0.0018 to 0.0028 mg/m^3. Exposure levels were estimated to have been 0 to 0.054 mg/m^3 in the preceding years (Barker et al. 1998).

At a vapour pressure of 0.15 hPa, the vapour saturation concentration is about 150 ml/m^3.

1   Toxic Effects and Mode of Action

Maleic anhydride has sensitizing effects on the airways in humans. Marked contact sensitizing effects were determined in animals under experimental conditions.

Irritation is the primary effect in humans and animals after inhalation exposure to maleic anhydride. Maleic anhydride leads to skin irritation and is corrosive to the eyes.

In a 6-month inhalation study in rats, hamsters and monkeys, irritation of the nasal cavity was observed at the lowest concentration tested of 0.27 ml/m^3. However, marked histopathological changes were found only in rats.

There is no evidence that maleic anhydride induces genotoxic effects, nor have prenatal toxicity or carcinogenic effects been demonstrated.

2   Mechanism of Action

The local effects of maleic anhydride on the mucous membranes are probably caused by reactions of the acid anhydride with cellular nucleophiles or its conversion to maleic acid by hydrolysis.

The sensitizing reactions in the airways are the result of the induction of an IgE-mediated specific immune response.

3   Toxicokinetics and Metabolism

3.1   Absorption, distribution, elimination

There are no new data available.

The values calculated for dermal absorption using mathematical models are hypothetical because of the rapid hydrolysis of maleic anhydride (see Section 5.2).

3.2   Metabolism

There are no data available.

4   Effects in Humans

There are no data for the end points reproductive toxicity, genotoxicity and carcinogenicity.

Single exposures

In humans, the lowest irritation threshold for maleic anhydride was determined to be 1.0 mg/m^3. Exposure at a concentration of 20 ml/m^3 (about 80 mg/m^3) induced irritation of the eyes, the nasal mucosa and the respiratory tract after 5 minutes. Only isolated symptoms were observed after exposure to 5 ml/m^3 (about 20 mg/m^3) for 4 hours (Chevron Corp. 1984 a; Greim 2000 a). Additional data that are available are values for the odour threshold (1.8 mg/m^3) and the irritation threshold (5.5 mg/m^3) (Ruth 1986).

Repeated exposure

Information on respiratory symptoms was collected by questionnaire from 401 (79%) persons from a cohort of 506 workers from 4 plants in Great Britain who were exposed to dicarboxylic anhydride, maleic anhydride, phthalic anhydride and trimellitic anhydride. The symptoms chest tightness, breathing difficulties and wheezy or whistling breathing sounds were evaluated as respiratory symptoms. The exposure data and the levels of exposure in the individual work areas were used to estimate both the "current" and earlier, "past range" exposure concentrations of the three acid anhydrides handled. In the 3 plants with exposure to a mixture of substances, phthalic anhydride was found to be the acid anhydride that was present in the highest concentrations (Barker et al. 1998; van Tongeren et al. 1995, 1998).

The arithmetic means of the exposure concentrations are shown in Table 1.

Tab. 1   Exposure concentrations of the acid anhydrides handled (Barker et al. 1998)

Exposure	Current	Past range
maleic anhydride	1.8–2.8 µg/m^3	0–54 µg/m^3
phthalic anhydride	8.9–61.9 µg/m^3	0.4–2500 µg/m^3
trimellitic anhydride	0.5–0.9 µg/m^3	0–554.4 µg/m^3

Thirty-four (8.8%) of the workers reported having developed respiratory symptoms after they began to be exposed to dicarboxylic anhydride. Six of the cases were workers who reported symptoms after being exposed at the current levels, and 28 were former workers who had been exposed at the past range levels, which were markedly higher in some cases. It is noteworthy that in one plant with 13 cases (11.3%) of respiratory symptoms, the workers were exposed only to trimellitic anhydride. The data do not indicate whether these 13 cases were exposed at the current or past levels. The authors set 3 exposure ranges for the total exposure to dicarboxylic anhydrides (< 10, 10 – < 100 and ≥ 100 µg/m^3), into which the respiratory symptoms were roughly categorized. Workers with/without symptoms were distributed as follows across the three exposure ranges: 12/80, 11/21 and 4/7. The assessment included only those workers with full-shift exposure. Atopy and smoking habits did not have a significant effect. The data for sensitizing effects are described in the Section "Allergenic effects" (Barker et al. 1998).

A study that investigated the workers (n = 92) of 2 chemical plants who were exposed to a mixture of maleic anhydride and other acid anhydrides found work-related symptoms in 56 workers. The symptoms were rhinitis, coughing, conjunctivitis, dyspnoea, haemorrhagic rhinitis and the formation of mucous. The exposure concentrations were not determined (Baur et al. 1995).

Serial examinations of workers who were exposed to a mixture of maleic anhydride and other coal tar processing products established a possible relationship between exposure to maleic anhydride and eosinophilia (Henschler 1992).

Conclusions: As exposure was to a mixture of substances in all studies, it can only be assumed that maleic anhydride was involved in the development of the respiratory effects observed in the workers. While phthalic anhydride induced

marked irritation of the upper respiratory tract of workers only at high levels of exposure (irritation at 4 ml/m³), in inhalation studies in rats, trimellitic anhydride induced irritation of the lungs at 0.00025 ml/m³, a much lower concentration than the levels at which effects were induced by maleic anhydride (ACGIH 2014 b, c; Greim 2000 b, available in German only; Greim 2009). On the basis of these data, it can be concluded that trimellitic anhydride was primarily responsible for the symptoms observed. A specific exposure–effect relationship for maleic anhydride cannot be derived from the data reported by these studies.

Local effects on skin and mucous membranes

A worker who was splashed with hot (60–100 °C) maleic anhydride suffered first and second degree burns to the skin, eye irritation with focal corneal erosions and respiratory tract irritation with mild rhonchi in all lung areas. Burning in the eyes, sensitivity to light, a dry cough and fatigue persisted for about 10 days. The skin burns healed within 14 days. Skin contact through clothing that was covered with maleic anhydride caused first to second degree burns to the skin in 2 workers. The skin lesions healed within 9 days (Henschler 1992).

Reports from 1938, 1946 and 1956 described irritation of the mucous membranes, skin rashes, eye pain, lacrimation and blurred vision in persons with occupational exposure. Data for the level of exposure are not available (Henschler 1992; Venables 1989).

Allergenic effects

Since the publication of the 1995 supplement (Greim 1998), a number of other findings have become available for the sensitizing effects on the skin and airways induced by maleic anhydride.

Sensitizing effects on the skin

In spite of the high reactivity of maleic anhydride, there is only little evidence of sensitizing effects on the skin in humans. On the one hand, this may be because of only very slight exposure of the skin, on the other hand, a number of the patch tests were carried out with vehicles that are not inert for maleic anhydride (see below).

A collective of 190 workers (126 enamellers and 64 decorators) from 5 ceramic factories underwent dermatological and allergological examination. Sensitization was determined in 48 workers, in 28 cases to nickel (II) salts. Maleic anhydride was one of the substances tested and yielded 2 positive reactions; however, these findings cannot be included in the assessment because ethanol was used as the vehicle. In addition, the extent of exposure to maleic anhydride at the factories cannot be determined from the data available (Motolese et al. 1993). The same is true for the 2 positive reactions obtained in patch tests performed on a collective of 50 enamellers, who were mainly involved in the manual production of glazes or decoration (Gaddoni et al. 1993). Neither study obtained a positive reaction with 1% phthalic anhydride; this acid anhydride was tested concurrently using petrolatum as a suitable vehicle. In an earlier study, 1 of 138 workers from 3 ceramic plants produced a reaction to the formulation with phthalic anhydride, while 3 of the workers exhibited reactions to a 1% maleic anhydride formulation in ethanol (Seidenari et al. 1990).

One worker who had been employed for 30 years at a plant manufacturing fibreglass-reinforced plastics had recurring eczema since beginning employment at the plant, particularly in the summer. He produced positive reactions in the patch test to both cobalt and to a polyester resin used at the plant. This resin contained maleic anhydride, phthalic anhydride and dicyclopentadiene in addition to cobalt naphthenate and other substances. Maleic anhydride was tested in the patch test as a 1% formulation in water and produced a questionable reaction after 72 hours; the same results were obtained with a 1% formulation of maleic acid in water. No reaction was yielded by phthalic anhydride and phthalic acid (both were tested as a 1% formulation in 70% ethanol), while a 2+ reaction was produced by a 1% formulation of fumaric acid in alcohol (Minamoto et al. 2002).

Initial symptoms of rhinitis, breathing difficulties and conjunctivitis, followed later by urticarial skin symptoms affecting the whole body including the head, were observed in a 32-year-old worker employed in a plant producing polyester resin after 3 years of employment. The worker filled reaction vessels with granulated maleic anhydride while wearing a protective helmet with a fresh air supply. There was also possible exposure to phthalic anhydride. Patch tests with 0.1% and 1% maleic and phthalic anhydride in petrolatum yielded negative results. A wheal with a diameter of 14 mm was induced in a prick test with a maleic anhydride–serum albumin conjugate. No reaction was observed 20 minutes after open application of this conjugate to the intact skin; wheals developed, however, after 40 minutes. An open patch test with 1% maleic anhydride in water (!) yielded negative results; rhinitis and wheals were observed at the test site and beyond 20 minutes after testing with the undiluted substance. In the radioallergosorbent test (RAST), specific IgE antibodies against the conjugate (9.4 kU/l; RAST rating 3) were determined (Kanerva and Alanko 2000). Apart from the cases previously described, a retrospective analysis of data collected from 1990 to 2006 in 21 patients with work-related contact urticaria determined only additional cases of contact urticaria induced by phthalic anhydride (2 cases), chlorendic acid (1 case) and methylhexahydrophthalic anhydride and methyltetrahydrophthalic anhydride (17 cases in total) (Helaskoski et al. 2009).

Overall, the findings available do not allow a definitive assessment of the contact allergenic effects induced by maleic anhydride in humans.

Sensitizing effects on the airways

In 2 plants, 92 workers (employed in the laboratory, production, packaging or transport) were exposed to at least one dicarboxylic anhydride, primarily pyromellitic dianhydride, phthalic anhydride and maleic anhydride, for varying lengths of time (0.6 to 41 years). Symptoms of the upper and lower respiratory tract were reported by 56 of the workers. In decreasing order of incidence, these were rhinitis (44×), coughing (24×), conjunctivitis (22×), dyspnoea (18×), haemorrhagic rhinitis (11×) and the formation of bronchial mucous (9×). In the enzyme allergo-sorbent test (EAST), specific IgE antibodies against the maleic anhydride–human serum albumin (HSA) conjugate were found in 6 of the symptomatic workers and in 1 asymptomatic worker. Specific IgE against 3 other dicarboxylic anhydrides were detected in 4 of the 6 symptomatic workers. In the 2 remaining symptomatic workers either IgE against 2 or 1 other dicarboxylic anhydride were determined. In a follow-up study carried out 10 months later, specific IgE against the maleic anhydride–HSA conjugate were still detected in 2 of 3 workers who were not exposed further to dicarboxylic anhydride (Baur et al. 1995).

In a study from 1992, 401 workers from a collective of 506 workers currently employed or previously employed for at least 1 month in 1 of 4 plants completed a questionnaire relating to their work and the symptoms arising during their employment. Of these, 173 were currently working in an area with potential exposure to dicarboxylic anhydride, 76 had changed workplaces within the plant and 152 had left the plants completely. Prick tests with the HSA conjugates of maleic anhydride, phthalic anhydride and trimellitic anhydride were performed in 378 of 401 persons. The employees of 3 plants were exposed mainly to phthalic anhydride, but also to trimellitic anhydride and maleic anhydride, while in 1 plant exposure was to trimellitic anhydride only. Workplace-related symptoms were reported by 33 of the 378 tested persons. Positive prick tests were obtained from 12 tested persons, 2 of whom did not have any symptoms. It was possible to relate sensitization to low levels of current exposure only in 1 case. Eight of the 12 persons were exposed only to trimellitic anhydride. In 2 plants, the current mean exposure levels to maleic anhydride were 2.8 and 1.8 μg/m^3 after 14 and 25 determinations, respectively. The past mean exposure levels in the 3 plants ranged from 0 to 5.4, 0 to 4.9 and 0 to 54 μg/m^3. The mean exposure levels determined for 4 specific work activities were 5.5 μg/m^3 (collection of samples/testing), 6.9 μg/m^3 (handling of the sacks), 10.8 μg/m^3 (finishing of the resins) and 17.3 μg/m^3 (filling) (range: 1.4 to 28.6 μg/m^3). From the data provided by the publication, it is not possible to determine how many of the positive prick test reactions were induced by a maleic anhydride–HSA conjugate. The authors set 3 exposure ranges for "dicarboxylic anhydrides" (< 10, 10 – < 100 and ≥ 100 μg/m^3), which they used to roughly categorize the results of the prick tests with dicarboxylic anhydride: 3 positive reactions and 199 negative results were obtained from the employees with the lowest levels of exposure, 7 positive reactions and 117 negative results from the employees with moderate levels of exposure and 2 positive reactions and 50 negative results from employees with the highest levels of exposure. Symptomatic and asymptomatic patients were assigned to the 3 exposure ranges as follows: 12/80, 11/21 and 4/7. The authors provided

a specific exposure matrix only for workers who had become sensitized to trimellitic anhydride. According to this, 6 of the 8 sensitized workers were exposed on average to a maximum of 40 μg/m³ (Barker et al. 1998). The correlations established for trimellitic anhydride cannot be extrapolated to maleic anhydride.

Occupational asthma caused by intermittent exposure to maleic anhydride over a period of 8 years was reported in the case of a 60-year-old worker employed in the insecticide manufacturing industry. The findings were objectified by determinations of the peak expiratory flow at the workplace and evidence of specific IgE (Hansen et al. 2014; in Danish, available only as an abstract).

5   Animal Experiments and in vitro Studies

5.1   Acute toxicity

5.1.1   Inhalation

An LC_{50} > 4350 mg/m³ was determined after 1-hour exposure of rats to maleic anhydride (ECHA 2015).

5.1.2   Oral administration

The LD_{50} for maleic anhydride after oral exposure of rats was between 235 and 1100 mg/kg body weight. LD_{50} values of 465 mg/kg body weight, 390 to 700 mg/kg body weight and 875 mg/kg body weight were obtained for mice, guinea pigs and rabbits, respectively. Effects were observed in the gastrointestinal tract, liver, kidneys and the lungs (Henschler 1992).

5.1.3   Dermal application

Occlusive application of maleic anhydride yielded LD_{50} values of 400 to 1000 mg/kg body weight in rabbits. Again, inflammation of the gastrointestinal tract was induced (Henschler 1992).

5.1.4   Intraperitoneal injection

The intraperitoneal LD_{50} for maleic anhydride in rats was 97 mg/kg body weight (Henschler 1992).

5.2   Subacute, subchronic and chronic toxicity

Maleic anhydride rapidly hydrolyses to maleic acid under aqueous conditions; the acid anhydride has a half-life of 22 seconds in water at 25 ℃. It is to be assumed that maleic anhydride and maleic acid were both present during the toxicity tests (OECD 2005). Maleic acid is irritating to the skin and highly irritating to the eyes (ECB 2000).

5.2.1   Inhalation

Inhalation exposure (3 to 5 exposures for 1 to 6 hours) at concentrations of 10 000 mg/m³ were lethal to cats, rabbits and guinea pigs; the causes of death were purulent bronchopneumonia and pulmonary oedema (no other details, Henschler 1992).

In a 4-week inhalation study, groups of 10 female and 10 male CD rats were exposed whole-body to maleic anhydride concentrations of 0, 12, 32 or 86 mg/m³ (0, 2.9, 7.8 or 21 ml/m³) for 6 hours per day, on 5 days per week. Irritation, inflammation, bleeding and hyperplasia were observed in the respiratory tract. The severity of the findings was dependent on the concentration. The effects in the eyes observed in the high concentration group did not occur in the other concentration groups. The exact data are shown in Table 2 (Henschler 1992; Monsanto Co 1984 b).

In an inhalation study, rats, hamsters and rhesus monkeys were exposed whole-body to maleic anhydride vapour at concentrations of 0, 1.1, 3.3 or 9.8 mg/m³ (sum of maleic anhydride and maleic acid) for 6 hours a day, on 5 days a week, for 6 months. Signs of irritation in the nose and eyes were observed in all exposed animals and increased with the concentration. Epithelial hyperplasia and squamous metaplasia in the nasal tissue were not determined in monkeys in the histopathological examination. No treatment-related findings were observed in the ophthalmological, haematological and clinico-chemical examinations and urinalysis. Slight irritation in the lungs was detected at the next higher concentration. Lung function tests were performed pre-treatment and after exposure for 3 or 6 months only in monkeys; these did not yield significant effects. The exact data are shown in Table 2 (Henschler 1992; Monsanto Co 1984 a; Short et al. 1988). The study was carried out in 1981. The original study report presented histological data only for the control group and the high concentration group. A later report included histopathological data for all groups, which were neither presented nor discussed in this form in the original report.

Tab. 2 Effects of maleic anhydride after repeated inhalation exposure

Species, strain, number per group	Exposure	Findings	References
rat, CD, 10 ♂, 10 ♀	**4 weeks**, 6 hours/day, 5 days/week, 0, 12, 32, 86 mg/m³ (0, 2.9, 7.8, 21 ml/m³) whole-body exposure	**12 mg/m³ and above**: upper respiratory tract: squamous metaplasia, trachea: inflammatory infiltrates in the mucosa, turbinates: inflammatory infiltrates in the mucosa and epithelial hyperplasia, lungs: intra-alveolar bleeding, foamy macrophages in the alveoli; **32 mg/m³ and above**: body weights ↓, feed consumption ↓ (only ♀), lungs: haemorrhagic foci, dark red foci, adhesion, congestion, bleeding, atelectasis, bronchial epithelial hyperplasia, squamous metaplasia, trachea: epithelial hyperplasia; **86 mg/m³**: reddish discharge from the eyes, nasal discharge with periodically recurring nosebleeds, increased salivation, effects reversible except for nasal discharge, upper respiratory tract and lungs: intensification of all effects, eyes: keratitis, corneal vascularization	Monsanto Co 1984 b
rat, CD, 15 ♂, 15 ♀	**6 months**, 6 hours/day, 5 days/week, 0, 1.1, 3.3, 9.8 mg/m³ (0, 0.27, 0.81, 2.4 ml/m³) whole-body exposure	**1.1 mg/m³: LOAEC**, irritation in the nose and eyes (no other data), body weight gains: ♀ ↓ (not significant), nasal cavity: epithelial hyperplasia of the mucosa of the septum and turbinates (♂: 8/15, ♀: 11/15, minimal to mild), squamous metaplasia (♂: 2/15), inflammation (focal to multifocal infiltration with neutrophilic granulocytes and eosinophils in the epithelium, minimal to mild); **3.3 mg/m³**: increased irritation in the nose and eyes (no other data), body weight gains ↓ (statistically significant only after 92 days in ♀), nasal cavity: epithelial hyperplasia of the mucosa of the septum and turbinates (♂: 15/15, ♀: 14/15, minimal to mild), squamous metaplasia (♂: 2/15, ♀: 2/15), exudate (1/15); **9.8 mg/m³**: reddish nasal discharge, eye discharge, sneezing, body weight gains ↓**, nasal cavity: epithelial hyperplasia of the mucosa of the septum and turbinates (♂: 12/15, ♀: 14/15, mild), squamous metaplasia (♂: 11/15, ♀: 13/15), exudate (3/15), spleen: ♀: haemosiderin in the red pulp ↑* (7/15, slight), prostate gland: ♂: interstitial lymphoid infiltrates (3/15, slight), acute prostatitis (1/15, mild)	Monsanto Co 1984 a; Short et al. 1988
hamster, Engle, 15 ♂, 15 ♀	**6 months**, 6 hours/day, 5 days/week, 0, 1.1, 3.3, 9.8 mg/m³ (0, 0.27, 0.81, 2.4 ml/m³) whole-body exposure	**1.1 mg/m³ and above: LOAEC**, irritation in the nose and eyes (no other data), nasal cavity: squamous metaplasia (♂: 2/15, ♀: 2/15); inflammation (focal to multifocal or diffuse infiltration with neutrophilic granulocytes and exudate, minimal to mild); **3.3 mg/m³**: increased irritation in the nose and eyes (no other data), nasal cavity: epithelial hyperplasia of the mucosa of the septum and turbinates (♂: 5/15, ♀: 8/15, minimal to mild), squamous metaplasia (♂: 1/15, ♀: 1/15); **9.8 mg/m³**: nasal discharge, dyspnoea (severe), gasping, nasal cavity: epithelial hyperplasia of the mucosa of the septum and turbinates (♂: 8/15, ♀: 5/15, mild), squamous metaplasia (♂: 8/15, ♀: 9/15)	Monsanto Co 1984 a; Short et al. 1988

Tab. 2 *(continued)*

Species, strain, number per group	Exposure	Findings	References
monkey, rhesus, 3 ♂, 3 ♀	**6 months**, 6 hours/day, 5 days/week, 0, 1.1, 3.3, 9.8 mg/m³ (0, 0.27, 0.81, 2.4 ml/m³) whole-body exposure	**controls**: <u>lungs</u>: fibrosis with mononuclear cell infiltrates (♂: 1/3, minimal); **1.1 mg/m³**: **LOAEC**, body weight gains ↓ (♂ statistically significant, not dependent on concentration), irritation in the nose and eyes (no other data), <u>nasal cavity</u>: inflammation (focal to multifocal infiltration with neutrophilic granulocytes in the mucosa and submucosa, minimal); **3.3 mg/m³**: body weight gains ↓ (♂ statistically significant, not dependent on concentration), ♂: brain weights ↓** (not dependent on concentration), <u>nasal cavity</u>: inflammation; **9.8 mg/m³**: body weight gains ↓ (♀ statistically significant, dependent on concentration), nasal discharge, eye irritation, dyspnoea (mild) with coughing and sneezing, <u>nasal cavity</u>: inflammation, <u>lungs</u>: fibrosis with mononuclear cell infiltrates (♂: 1/3, mild, ♀: 2/3, minimal to mild), interstitial inflammation (♀: 1/3, mild)	Monsanto Co 1984 a; Short et al. 1988

$^*p < 0.05$, $^{**}p < 0.01$

Conclusions: After inhalation exposure for 6 months, irritation in the nasal cavity was observed in all 3 species even at the lowest concentration tested of 1.1 mg/m³ (about 0.27 ml/m³). The LOAEC was therefore 1.1 mg/m³ (about 0.27 ml/m³). A NOAEC cannot be derived from these studies.

5.2.2 Oral administration

The high reactivity of maleic anhydride and its tendency to hydrolyse give rise to uncertainty with respect to its stability and the actual dose of the substance in the feed.

Dogs ingested capsules containing maleic anhydride at dose levels of 0, 60, 120 or 180 mg/kg body weight and day. After 14 days, severe effects in the gastrointestinal tract leading to death were induced in several of the animals at doses of 120 mg/kg body weight and above. In a 90-day study, maleic anhydride given with the feed caused kidney damage in rats at the dose level of 100 mg/kg body weight and day and haematological effects in male dogs at 60 mg/kg body weight and day. NOAELs of 40 mg/kg body weight and day for rats and male dogs and of 60 mg/kg body weight and day for female dogs were derived from the study data. In a 6-month feeding study, severe kidney and liver damage was induced in rats at the lowest dose tested of 250 mg/kg body weight and day and above (Henschler 1992).

In a multigeneration study, maleic anhydride in corn oil was given to CD rats (10 males and 20 females per dose group) in gavage doses of 0, 20, 55 or 150 mg/kg body weight and day for 80 days. Rhonchi were observed in the F0 and F1 generations which intensified with the dose. Increased mortality was determined in the high dose group. The increased mortality observed in the low dose group of the F1 generation was attributed to injuries sustained during gavage treatment. Interstitial pneumonia was determined to be the cause of death for 1 animal. In the high dose group of the F0 generation, kidney damage (necrosis of the renal cortex) was determined in 60% of the males and 15% of the females. A significant increase in the absolute kidney weights of 108% and 111% was observed in the female rats of the low and medium dose groups, respectively (Henschler 1992; Monsanto Co 1982; Short et al. 1986). It was not possible to derive a NOAEL from this study.

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

When moist, maleic anhydride is irritating to the skin (Henschler 1992).

Maleic anhydride (500 mg, finely ground) was applied semi-occlusively to the shaved skin of groups of 6 New Zealand White rabbits for an exposure period of 4 hours. Analyses were carried out 4, 24, 48 and 72 hours and 7 days after the removal of the substance. Severe erythema and scabbing (grade 4 of 4) and the development of mild to severe oedema (grade 2–4 of 4) continued to be observed 7 days after treatment (Chevron Corp. 1984 b).

5.3.2 Eyes

Maleic anhydride was corrosive to rabbit eyes and induced irreversible damage (Henschler 1992). In a study that investigated the irritation induced in the eyes of New Zealand White rabbits, maleic anhydride (0.1 g, undiluted) was corrosive to the eyes with an irritation index of 107 of 110 (ACGIH 2014 a; OECD 2005).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

Positive results were obtained in a local lymph node assay (LLNA) with formulations of maleic anhydride in acetone/ olive oil (4:1). In deviation from OECD Test Guideline 429, the tests were carried out with female BALB/c mice instead of CBA/Ca mice. Tritium-labelled methylthymidine was injected on day 5 instead of day 6. The stimulation indices calculated for the 0.1%, 0.25%, 0.5%, 1% and 2% test formulations were about 1.9, 4.9, 6.3, 14.0 and 15.9, respectively, and a value of 0.16% was determined for the test concentration that led to a threefold increase in lymphocyte proliferation (EC3 value). Four other dicarboxylic anhydrides likewise yielded positive results with largely similar EC3 values (Dearman et al. 2000).

Clearly positive results were obtained with maleic anhydride in a Buehler test in 20 Crl:(HA)BR guinea pigs. The animals were occlusively treated for induction with 5% maleic anhydride in paraffinum liquidum (white mineral oil) and for the challenge with a 0.5% formulation in the same vehicle. Eight of the animals responded to the challenge treatment with a (very) weak reaction (grade 0.5) and 12 animals with a marked reaction (grade 1–2) (OECD 2005).

In another Buehler test, groups of 5 Hartley guinea pigs were treated for induction with 0.1% (A), 1% (B) or 5% (C) maleic anhydride in acetone. None of the animals (groups A and B) and 3 and none of the animals (group C) responded to the challenge with 10% and 1% maleic anhydride, respectively. A repeat challenge was carried out with both concentrations in groups B and C; only 2 animals in group C produced reactions at the higher test concentration. The 5 control animals did not respond to treatment with either of the two formulations (Nakamura et al. 1999).

In a maximization test, groups of 5 Hartley guinea pigs received both intradermal and topical induction treatment with 0.0001% (A), 0.001% (B), 0.01% (C), 0.1% (D) or 1% (E) maleic anhydride in acetone. Prior to the topical induction treatment, the animals were treated non-occlusively with 10% sodium lauryl sulfate in petrolatum. The challenge treatment was carried out with 10% and 1% formulations of maleic anhydride in acetone. Reactions were obtained in 3 and none of the animals (group A), in 5 and 3 animals (both in group B and C) and in all 5 animals with both formulations (both in group D and E), respectively. The 5 control animals did not respond to treatment with either of the two formulations (Nakamura et al. 1999).

Positive results were obtained also in an adjuvant patch test carried out with groups of 5 Hartley guinea pigs. In this test, the animals were first treated by intradermal injection with Freund's adjuvant, followed 24 hours later by the occlusive application of 0.1 ml of a maleic anhydride formulation in acetone to previously abraded skin at the injection site in concentrations of 0.01% (A), 0.1% (B), 1% (C) or 10% (D). At the challenge treatment after 14 days with 10% and 1% maleic anhydride, reactions were obtained in none of the animals (group A), in 1 and none of the animals (group B), in

5 animals at each concentration (group C) and in 5 and 3 animals (group D), respectively. A second challenge treatment was carried out with both concentrations in groups B to D; reactions were observed in 2 animals at each concentration (group B), in 5 animals and 1 animal (group C) and in 5 and 3 animals (group D), respectively. The 5 control animals did not respond to treatment with either of the two formulations (Nakamura et al. 1999).

Positive results were obtained with maleic anhydride in the human cell line activating test (h-CLAT) in an in vitro study with monocytic THP-1 leukaemia cells, but only with regard to CD54 expression and not for CD86 expression (no other details, Nukada et al. 2011).

Conversely, negative results were obtained with maleic anhydride and, among other substances, with trimellitic anhydride, hexamethylene diisocyanate and glutaraldehyde in an in vitro test with the human epithelial skin cell line NCTC 2544 (Corsini et al. 2013).

Publications describing QSAR models listed maleic anhydride as a potential skin sensitizer (Li et al. 2007). Unlike trimellitic anhydride, phthalic anhydride and hexahydrophthalic anhydride, maleic anhydride was found to undergo Michael addition reactions with SH groups. Therefore, marked contact sensitizing effects are to be expected (Roberts and Patlewicz 2014).

In the direct peptide reactivity assay, dicarboxylic anhydrides were found to react primarily with the lysine groups of the tested peptides. However, it was noted that a relatively large fraction of maleic anhydride underwent reactions with the thiol residues of cysteine groups (Lalko et al. 2012).

5.4.2 Sensitizing effects on the airways

In comparison with the contact allergen 2,4-dinitrochlorobenzene (DNCB), maleic anhydride, like trimellitic anhydride, produced lower levels of γ-interferon and interleukin-12 in a modified LLNA, but higher levels of the TH2-type cytokines interleukin-10 and interleukin-4 (see above) (Dearman et al. 2000). In another study, the treatment of BALB/c mice with maleic anhydride (again) in comparison with DNCB led to a lower increase in γ-interferon and interleukin-12 secretion. In comparison with trimellitic anhydride, maleic acid led only to a slight increase in interleukin-4 secretion, while interleukin-5, interleukin-10 and interleukin-13 secretion was markedly higher (Dearman et al. 2002).

BALB/c mice were treated with formulations containing 2.5% dicarboxylic anhydride on days 1 and 6, followed by application to the ears on days 10, 11 and 12. The auricular lymph nodes were removed on day 14 and the mRNA expression levels were determined for a number of cytokines. Maleic anhydride and to a much lesser degree phthalic anhydride and trimellitic anhydride, but not hexahydrophthalic anhydride, induced (low) levels of interleukin-4 production. By contrast, all acid anhydrides led to the slightly reduced expression of interleukin-10 and interleukin-13 after treatment. No changes in the expression of interleukin-2, interleukin-3, interleukin-5, interleukin-9, interleukin-15 and γ-interferon were determined (Plitnick et al. 2003).

In an LLNA protocol that included the removal of the auricular lymph nodes on day 6 of testing, stimulation indices of about 38, 54 and 49 were calculated following the application of 2.5%, 5% and 10% maleic anhydride, respectively, to CBA/JHsd mice. The application of 10% maleic anhydride or trimellitic anhydride and of 15% phthalic anhydride or hexahydrophthalic anhydride induced a marked increase in interleukin-4, interleukin-10 and interleukin-13 production; this was slightly less marked in the case of maleic anhydride in comparison with the other acid anhydrides (Plitnick et al. 2003).

5.5 Reproductive and developmental toxicity

In a combined teratogenicity and 2-generation reproduction study in rats with gavage administration, no signs of developmental toxicity and maternal toxicity were observed in the developmental toxicity study, which used a protocol similar to that of OECD Test Guideline 414, up to the highest dose tested of 140 mg/kg body weight and day. The 2-generation reproduction study investigated doses of 0, 20, 55 and 150 mg/kg body weight and day; reduced body weights were observed in the F1 generation at 150 mg/kg body weight and day. The NOAEL for foetotoxicity was 55 mg/kg body

weight and day (see Section 5.2.2; Henschler 1992; Monsanto Co 1982). Prenatal toxicity was not observed in mice in studies with intraperitoneal administration (see Section 5.2.2; Henschler 1992; Monsanto Co 1982).

No teratogenic effects were observed after intraperitoneal administration of maleic anhydride (dosage not specified) to pregnant CD-1 mice on gestation days 8 to 10 or 11 to 13, while equimolar amounts of succinic anhydride and phthalic anhydride induced teratogenic effects (statistically significant increase in the incidence of abnormal ribs and vertebrae and cleft palates) (Dixon et al. 1978; Henschler 1992). The data for this study are available only in the form of an abstract.

These findings are contradicted in another abstract from the same research group describing a study with intraperitoneal administration of maleic anhydride which led to teratogenic effects in CD-1 mice in the form of foetal abnormalities at the minimum dose of 0.375 mmol/kg body weight (no other details, ACGIH 2014 a; Brown et al. 1978).

In general, however, the validity of data derived from developmental toxicity studies with exposure by intraperitoneal routes of administration is only very limited.

5.6 Genotoxicity

5.6.1 In vitro

In vitro, maleic anhydride did not demonstrate genotoxic potential in the bacterial strains TA98, TA100, TA1535, TA1537 and TA1538 (Henschler 1992). A slight, but not significant, increase in revertants was observed only in the strain TA102 (Aeschbacher et al. 1989; Monsanto Co 1984 c). Chromosomal aberrations produced in a hamster fibroblast cell line with maleic anhydride can be regarded as non-specific because effects resulting from the acidity of maleic acid cannot be excluded as the study conditions were insufficiently documented (Henschler 1992; OECD 2005).

In an HPRT gene mutation test in V79 cells carried out according to OECD Test Guideline 476, maleic anhydride did not induce gene mutations either with or without the addition of metabolic activation (S9 mix). The concentrations tested in the 2 experiments were 0, 37.5, 75, 150, 300, 600 or 1200 µg/ml and 0, 75, 150, 300, 600, 900 or 1200 µg/ml, respectively (ECHA 2015).

5.6.2 In vivo

The number of chromosomal aberrations was not increased in the bone marrow of SD rats after inhalation exposure to maleic anhydride concentrations of 0, 1, 10 or 100 mg/m³ for 6 hours. No differences in the mitotic index between the treated and the control groups were observed. Therefore, there was no evidence of cytotoxicity. The temperature in the exposure chamber ranged from 23 to 25 ℃ at 36% to 45% humidity. Under these conditions, more than 50% of the maleic anhydride was converted to maleic acid by hydrolysis (Henschler 1992; Monsanto Co 1983).

5.7 Carcinogenicity

In a 2-year carcinogenicity study, the tumour incidence was not increased in F344 rats given maleic anhydride with the feed at doses of 10 to 100 mg/kg body weight and day (Henschler 1992).

6 Manifesto (MAK value/classification)

The critical effects induced by maleic anhydride after exposure by inhalation are irritation to the respiratory tract in humans and animals and sensitizing effects on the respiratory tract and the skin.

MAK value. Insufficient data are available in humans for maleic anhydride. It was not possible to draw conclusions about the effects induced solely by maleic anhydride from a study with workers in polyester resin production with

exposure to a mixture of maleic anhydride and 2 other acid anhydrides (Barker et al. 1998). Therefore, the MAK value is derived on the basis of data from animal studies.

In an inhalation study with exposure of rats, hamsters and monkeys to maleic anhydride for 6 months, irritation to the nose and eyes was observed in all 3 species at the lowest concentration tested of about 0.27 ml/m^3 (1.1 mg/m^3). The findings in monkeys exposed to a maleic anhydride concentration of 0.27 ml/m^3 (1.1 mg/m^3) indicate irritant effects that go beyond sensory irritation. Inflammation indicators were observed that were assessed as only minimal (see Section 5.2.1; Table 2) but are the initial signs of processes that go beyond neurogenic inflammation. Therefore, they cannot be compared directly with effects regarded as adverse which can be observed in volunteers under experimental conditions.

Although no new data are available, a much lower MAK value was derived using the method developed by Brüning et al. (2014), which takes these uncertainties into account. A NAEC (no adverse effect concentration) of 0.09 ml/m^3 (1:3) was extrapolated from the LOAEC of about 0.27 ml/m^3 (1.1 mg/m^3). Using the method proposed by Brüning et al. (2014) for the extrapolation of local irritation to the person (1:3), and taking the Preferred Value Approach into account, the MAK value is calculated to be 0.02 ml/m^3 (0.081 mg/m^3) because an intensification of the effects is not to be expected after chronic exposure.

Peak limitation.   As the MAK value was derived primarily on the basis of the induced irritation, the substance remains classified in Peak Limitation Category I with an excursion factor of 1 (see Greim 2000 a).

Now-obsolete studies in humans with a number of uncertainties reported thresholds between 1 and 20 mg/m^3 (about 0.25–5 ml/m^3) for maleic anhydride. However, the validity of the observations in humans is considered to be very limited. Maleic anhydride is sensitizing to the airways, but quantitative data are not available for the concentration levels at which sensitization is induced. In analogy to the momentary values set for the isocyanates (2-fold MAK value), which are sensitizing to the airways, a momentary value of 0.05 ml/m^3 has been established for maleic anhydride.

Prenatal toxicity.   In the developmental toxicity study in rats, no effects were induced up to the highest dose tested of 140 mg/kg body weight and day. In the generation study in rats, the foetal weights were reduced in the F1 generation at 150 mg/kg body weight and day. The NOAEL for foetotoxicity was 55 mg/kg body weight and day.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL for developmental toxicity of 140 mg/kg body weight and day and the NOAEL for foetotoxicity of 55 mg/kg body weight and day in rats to a concentration in workplace air: the corresponding species-specific correction values for the rat (1:4), the assumed oral absorption of 100%, the body weight (70 kg) and the respiratory volume (10 m^3) of the person and the assumed 100% absorption by inhalation. The concentrations calculated from this are 245 and 96.3 mg/m^3, respectively. This results in 2988-fold and 1174-fold margins between these values and the MAK value of 0.02 ml/m^3 (0.081 mg/m^3) and classification in Pregnancy Risk Group C has been retained for maleic anhydride.

Germ cell mutagenicity.   A mutagenic potential was not determined in vitro in Salmonella typhimurium and in V79 cells. Chromosomal aberrations were not induced in vivo. Therefore, a genotoxic potential is not suspected and the substance has not been classified in any of the categories for germ cell mutagens.

Absorption through the skin.   The dermal LD$_{50}$ is below 1000 mg/kg body weight; however, the substance is severely irritating to the skin, which means that the skin barrier may have been destroyed during the test. As a result of hydrolysis, it is not expedient to apply the models to calculate the amount absorbed through the skin. Longer periods of unnoticed contact with the skin are unlikely to occur because of the probable severe irritation to the skin. For this reason, maleic anhydride has not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization.   Maleic anhydride is sensitizing to the airways in humans. However, there are no valid clinical findings for contact sensitization. Marked contact sensitizing effects were derived from the clearly positive results reported by studies carried out with guinea pigs and mice under experimental conditions. For this reason, maleic anhydride remains

designated with both "Sh" and "Sa" (for substances which cause sensitization of the skin or airways). A recently published study was not able to establish a sufficient correlation between exposure and the incidence of disease. Therefore, it is still not possible to determine the concentration level at which sensitization of the airways may occur or the concentration level below which an allergic reaction in the airways will not occur.

Notes

Competing interests

The established rules and measures of the commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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