



Danish Ministry of the Environment  
Environmental Protection Agency

**Evaluation of health hazards by exposure to**

**Maleic anhydride**

**and proposal of a health-based quality  
criterion for ambient air**

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**Title:**

Evaluation of health hazards by exposure to Maleic anhydride and proposal of a health-based quality criterion for ambient air

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Sources must be acknowledged.

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# Preface

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to maleic anhydride and proposal of a health based quality criterion for ambient air. This resulted in 2006 in the present report, which was prepared by Grete Østergaard, Elsa Nielsen and Ole Ladefoged, Department of Toxicology and Risk Assessment, Danish Institute for Food and Veterinary Research, i.e. the present Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

The report has been subjected to review and discussion and has been endorsed by a steering committee consisting of representatives from the following Danish authorities:

The Danish Working Environment Authority,  
The Danish Ministry of Food, Agriculture and Fisheries (The Faculty of Agricultural Sciences),  
The Danish Veterinary and Food Administration,  
The National Board of Health, Denmark,  
The Danish Environmental Protection Agency

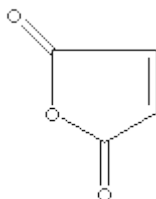
The Danish Environmental Protection Agency  
Copenhagen, September 2013.

# 1 General description

## 1.1 Identity

Molecular formula:  $C_4H_2O_3$

Structural formula:



Molecular weight: 98.06

CAS-no.: 108-31-6

Synonyms: Maleic anhydride  
2,5-furandione  
Toxic anhydride  
cis-Butenedioic anhydride

## 1.2 Physical / chemical properties

Description: Colourless needles or white crystalline solid with an acrid odour.

Purity: -

Melting point: 53 °C

Boiling point: 202 °C (sublimates)

Density: 1.48 g/cm<sup>3</sup> (at 20 °C)

Vapour pressure: Various values are reported at 20°C:

Table 1. Vapour pressures of maleic anhydride

Pascal (Pa)	mm Hg	Calculated concentration of saturated vapours (mg/m <sup>3</sup> )	Reference
0,006	0,000045	0,24	IUCLID, 2000
0,0066	0,00005	0,27	IUCLID, 2000
2	0,015	80,5	IUCLID, 2000
20	0,15	805	IUCLID, 2000
0,0066	0,00005	0,27	HSDB, 2001
21	0,16	859	HSE, 1996

Concentration of saturated vapours:	Please see Table 1 for calculated values based on the various reported vapour pressures.
Vapour density:	3.38 (air = 1)
Conversion factor:	1 ppm = 4.08 mg/m <sup>3</sup> (at 20 °C and 760 mmHg) 1 mg/m <sup>3</sup> = 0.25 ppm
Flash point:	103 °C
Flammable limits:	1.4 - 38.6 (v/v% in air)
Auto ignition temp.:	477 °C
Solubility:	Water: 550 g/l (at 20 °C)
logP <sub>octanol/water</sub> :	According to information in IUCLID, maleic acid reacts slowly with water and with n-octanol, so the partition coefficient log P <sub>ow</sub> cannot be determined.
Henry's constant:	-
pK <sub>a</sub> -value:	Maleic acid: 1.83
Stability:	-
Incompatibilities:	-
Odour threshold, air:	5 mg/m <sup>3</sup> (Chevron Corp. 1984, quoted from MAK 1995), 1.9 mg/m <sup>3</sup> (Ruth 1986), 1.3-1.7 mg/m <sup>3</sup> (IUCLID 2000).

### 1.3 Production and use

Maleic anhydride is mainly produced by the vapour phase oxidation of hydrocarbons over a solid catalyst. The substance is supplied in either molten or solid forms (dust suppressed briquettes or flake). Maleic anhydride is an intermediate, which is used in a wide range of products. The principal use of maleic anhydride is in the manufacture of unsaturated polyester resins. Other uses include the manufacture of oil additives, malic acid, and paper sizing resins. (HSE 1996).

### 1.4 Environmental occurrence

According to information in IUCLID (2000), maleic anhydride has not been found in the environment. The substance will hydrolyse with moisture in air or soil.

### 1.5 Environmental fate

No data have been found.

## 1.6 Human exposure

No data have been found on human exposure via the environment. Humans may be exposed occupationally.



## 2 Toxicokinetics

Very little toxicokinetic information is available.

### 2.1 Absorption

#### 2.1.1 Inhalation

Signs of central nervous system depression were observed in rats in a single-dose inhalation study, indicating that absorption occurs via this route (Monsanto 1983 – quoted from HSE 1996). For study details, please see section 4.1.1.

#### 2.1.2 Oral intake

In acute oral toxicity studies, maleic anhydride exhibits toxic properties, indicating that absorption occurs (HSE 1996).

A study of plasma levels in dogs following long-term (90 days) dietary administration of maleic anhydride at a concentration of 60 mg/kg b.w indicates that the substance is absorbed via this route. Plasma concentrations were measured on day 1, 3, 12, 29 and 90. It was calculated that a steady plasma level was reached after 55 days. In male dogs the plasma concentration was 1.8-3.5 µg/l (Dow Chemical Co. 1984 – quoted from HSE 1996).

#### 2.1.3 Dermal contact

Maleic anhydride has a rather low order of toxicity via the dermal route indicating limited absorption via this route (HSE 1996).

### 2.2 Distribution

No information is available.

### 2.3 Elimination

Maleic anhydride is known to undergo rapid hydrolysis to maleic acid on contact with water, and it is likely that maleic acid is the major breakdown product (HSE 1996).

### 2.4 Mode of action

No information has been found.

## 3 Human toxicity

### 3.1 Single dose toxicity

No data regarding single dose toxicity in humans have been found.

### 3.2 Irritation

#### 3.2.1 Skin irritation

A number of reports indicate that maleic anhydride is irritating to skin. First to second degree skin burns and itching, which became more severe on showering, were reported in two workers exposed by contact with contaminated clothing. (Merlevede & Elskins 1957, Union Carbide Corporation 1984 – both quoted from HSE 1996).

#### 3.2.2 Eye irritation

Maleic anhydride as dust or vapour has been reported to cause conjunctivitis, inflammation and swelling of the eyelids, severe lachrymation and photophobia (Merlevede & Elskins 1957, Ghezzi & Scotti 1965, Union Carbide Corporation 1984 – all quoted from HSE 1996).

According to data presented in IUCLID (2000), exposure to a concentration of 6-8 mg/m<sup>3</sup> (form of test material not described) resulted in eye irritation within 15 minutes (ACGIH 1986 – quoted from IUCLID 2000).

#### 3.2.3 Respiratory irritation

Two cases of respiratory irritation following exposure to maleic anhydride dust or vapour have been reported (Ghezzi & Scotti 1965 – quoted from HSE 1996).

A threshold of 5.48 mg/m<sup>3</sup> for irritative effects has been reported in a review by Ruth (1986).

According to data presented in IUCLID (2000), exposure to a concentration of 6-8 mg/m<sup>3</sup> (form of test material not described) resulted in nasal irritation within 1 minute; among workers repeatedly exposed to 5-10 mg/m<sup>3</sup>, ulceration of nasal mucous membrane, chronic bronchitis and in some cases asthma occurred (NIOSH 1978 – quoted from IUCLID 2000).

An exposure chamber study in male volunteers (age 22-27 years) has been performed. Maleic anhydride vapour was produced by melting the solid; exposure concentrations were determined by atmospheric analysis. Three sets of investigations were performed (Chevron Corporation 1960 – quoted from HSE 1996): In the first set of trials (6 trials, twice/week), groups of 2-7 volunteers were exposed for 5 minutes to concentrations ranging from 22 to 270 mg/m<sup>3</sup>. In the second set, 6 volunteers were exposed to a concentration of 54 mg/m<sup>3</sup> for 1 hour. In

the third set, 5 volunteers were exposed to 45 mg/m<sup>3</sup> for 1 hour. The volunteers described their sensory responses on a standard form at regular intervals throughout the exposure periods:

Table 2. Sensory response of volunteers exposed to maleic anhydride.

Concentration (mg/m <sup>3</sup> )	Description of sensory response
270	Nasal irritation, impairment of smell, eye irritation, greater than moderate pulmonary discomfort in 3/5 subjects.
179	Eye irritation, moderate pulmonary discomfort in 1/5 subjects.
54	Very occasional pulmonary discomfort and impairment of smell.
45	Very occasional pulmonary discomfort and impairment of smell.
22	Response not described in HSE (1996).

### 3.3 Sensitisation

Among 166 epoxy resin workers tested in a patch test, a single positive reaction was found (Nava et al. – quoted from HSE 1996).

### 3.4 Repeated dose toxicity

Only data regarding effects following inhalation have been found.

Repeated exposure to maleic anhydride may be associated with asthma. A number of case reports are summarised in Table 1. Nine cases have been described in 5 publications. In seven of the nine cases, a relation between asthma and maleic anhydride was demonstrated by positive response to a challenge exposure. It is not known whether the immune system is involved in the development of maleic anhydride-related asthma. No quantitative exposure data are available.

### 3.5 Toxicity to reproduction

No data have been found.

### 3.6 Mutagenic and genotoxic effects

No data have been found.

Table 3. Case reports of asthma related to maleic anhydride

Case	Symptoms	Evidence of causal association	Reference
1 worker	Respiratory problems in the afternoon, asthma attacks in evening	Epoxy fumes caused immediate response	Guerin et al. (1980 – quoted from HSE 1996)
4 workers	Not reported	Inhalation of maleic anhydride caused late asthmatic reaction in 3 workers	Graneek et al. (1986 – quoted from HSE 1996)
2 workers	Maleic anhydride associated asthmatic symptoms	Inhalation of maleic anhydride caused immediate and late asthmatic reaction; negative reaction to control (lactose) challenge	Durham et al. (1987), Graneek et al. (1987) (both quoted from HSE 1996)
1 worker	Asthmatic symptoms	Inhalation of maleic anhydride caused immediate and late asthmatic reaction	Lee et al. (1991 – quoted from HSE 1996)
1 worker	Asthma and haemolytic anaemia	No challenge performed	Gannon et al. (1992), Jackson & Jones (1993) (both quoted from HSE 1996)

### 3.7 Carcinogenic effects

No data have been found.

# 4 Animal toxicity

## 4.1 Single dose toxicity

### 4.1.1 Inhalation

Groups of 15 male and 15 female Sprague-Dawley rats were exposed to maleic anhydride vapour for 6 hours at average concentrations of 5 (range 4.5-6.3) or 164 (range 117-199) mg/m<sup>3</sup>. No animals died. All animals appeared sluggish during exposure. At the highest concentration many animals were observed to have squinted eyes and blood-encrusted noses. (Monsanto 1983 – quoted from HSE 1996).

### 4.1.2 Oral intake

Two briefly reported rat studies are available. In the first, oral LD<sub>50</sub>-values of 409 mg/kg for males and 235 mg/kg for females were reported. In the second study, no deaths were observed at 300 mg/kg, while all rats died at 1000 mg/kg. (Dow 1984 – quoted from HSE 1996).

### 4.1.3 Dermal contact

A dermal LD<sub>50</sub>-value of 2620 mg/kg (95% confidence limits 1930-3550 mg/kg) was determined in groups of 3 rabbits following a 24-hour exposure period (Vernot et al. 1977 – quoted from HSE 1996).

## 4.2 Irritation

### 4.2.1 Skin irritation

A 500 mg aliquot of maleic anhydride powder was applied to two sites on the back of each of 6 New Zealand White rabbits and covered with an occlusive dressing for 4 hours. Evidence of severe skin irritation was apparent throughout a 7-day observation period. Histopathological examination of the treatment sites demonstrated the presence of granulation tissue down to the muscle in one animal. (Chevron Corporation 1976 – quoted from HSE 1996).

### 4.2.2 Eye irritation

In rabbits, application of 0.005 ml of a 1% solution was highly irritating (Carpenter & Smyth 1946 – quoted from HSE 1996).

Ocular irritation caused by maleic anhydride vapour was seen at all treatment levels in a four-week rat study (0, 12, 32, 86 mg/m<sup>3</sup>, 6 hours/day, 5 days/week) (Monsanto Company undated – quoted from HSE 1996).

In rats, hamsters, and Rhesus monkeys exposed to by maleic anhydride vapour (0, 1.1±0.6, 3.3±0.6, 9.8±1.8 mg/m<sup>3</sup>, 6 hours/day, 5 days/week for 6 months), ocular irritation was seen at all treatment levels (Short et al. 1988).

### 4.2.3 Respiratory tract irritation

Evidence of respiratory irritation has been observed in repeated dose inhalation studies.

In a four-week rat study (0, 12, 32, 86 mg/m<sup>3</sup>, 6 hours/day, 5 days/week), clinical signs of respiratory irritation included nasal discharge, periodic nasal bleeding, and respiratory distress. In the nasal turbinates and trachea, concentration-dependent epithelial hyperplasia and presence of inflammatory exudate were found. Lesions in the lungs included increased incidence of haemorrhagic lung foci, epithelial hyperplasia, squamous metaplasia, and intraalveolar haemorrhage. The severity of microscopic changes was generally described as slight to moderate. There was no concentration without effect. (Monsanto Company undated – quoted from HSE 1996).

In rats, hamsters, and Rhesus monkeys exposed to by maleic anhydride vapour (0, 1.1±0.6, 3.3±0.6, 9.8±1.8 mg/m<sup>3</sup>, 6 hours/day, 5 days/week, for 6 months), respiratory irritation was seen at all treatment levels. The severity of signs was concentration-dependent and included nasal discharge, dyspnoea, gasping, coughing and sneezing. Pathological changes were only observed in the nose and included squamous cell metaplasia and epithelial hyperplasia in rats and hamsters, and inflammatory changes in all three species. Pulmonary function was tested in the monkeys, and was not affected. (Short et al. 1988).

The effects on the lungs of inhalation of maleic anhydride as a particulate aerosol at a target concentration of 500 microgram/m<sup>3</sup> 6 hours/day for 5 days have been examined in rats. No treatment-related macroscopic or microscopic lung changes were found. In a second experiment, rats were similarly exposed to maleic anhydride followed by a challenge with trimellitic anhydride at a concentration of 317 microgram/m<sup>3</sup>. Elevated numbers of haemorrhagic lung foci and microscopic lung lesions were found in two animals in each group. These experiments are described in further detail in section 4.4.1. (Amoco 1991 – quoted from HSE 1996).

## 4.3 Sensitisation

No relevant studies examining the skin or respiratory sensitising potential of maleic anhydride in animals have been found.

## 4.4 Repeated dose toxicity

### 4.4.1 Inhalation

Rats (10/sex/group) were exposed 6 hours/day, 5 days/week for 4 weeks via inhalation to maleic anhydride at 0, 12, 32 or 86 mg/m<sup>3</sup>. Nasal and ocular irritation was found at all concentrations, the severity was dose dependent with ocular and nasal discharge, periodic nasal bleeding and respiratory distress at the highest concentration. Also in the highest dose group, keratitis or corneal vascularisation was found, this was considered a local effect by the authors. At the two highest concentrations, body weight gain was reduced and the incidence of haemorrhagic foci was in-

creased. Epithelial hyperplasia was found in the nasal turbinates, trachea, and lungs. In the lungs, squamous metaplasia and intra-alveolar haemorrhage was present. The incidence was concentration-dependent, and the severity of the microscopic changes was generally described as mild or moderate. There was no dose level without effect. In this study, 12 mg/m<sup>3</sup> was a LOAEL for nasal and ocular irritation and respiratory tract lesions. (Monsanto Company undated – quoted from HSE 1996).

Rats (15/sex/group), hamsters (15/sex/group), and rhesus monkeys (3/sex/group) were exposed 6 hours/day, 5 days/week for 6 months via inhalation to maleic anhydride in mean analytical concentrations of 0, 1.1, 3.3 or 9.8 mg/m<sup>3</sup>. Dose-related signs of nasal and ocular irritation including discharge, sneezing, gasping, and coughing, were observed at all concentrations in all three species. In mid- and high-dose rats a reduction in body weight was found. No treatment-related effects were found in haematology, clinical chemistry, and urinalysis. No effect of treatment was found on pulmonary function in monkeys assessed before exposure and following 3 and 6 months of exposure. Histopathological examination revealed mild hyperplasia, metaplasia, and inflammation of nasal tissues in rats and hamsters, while monkeys only exhibited inflammatory changes. No concentration was without effect. The only histopathological finding in other tissues was an increased amount of haemosiderin pigment in the red pulp from spleens in female rats. This could not be explained, as there was no evidence of increased red cell destruction. In this study, 1.1 mg/m<sup>3</sup> was a LOAEL for nasal and ocular irritation and respiratory tract lesions. (Short et al. 1988).

The lung and IgG antibody response to short-term repeated inhalation has been investigated (Amoco 1991 – quoted from HSE 1996).

A group of 10 rats/sex was exposed to maleic anhydride as a particulate aerosol at a target concentration of 500 microgram/m<sup>3</sup>, 6 hours/day for 5 days. Two similar groups were not exposed. After a three-week rest period the exposed group and one of the unexposed groups received a 6-hour challenge exposure to a similar concentration of maleic anhydride. The third group was not challenged. About 18 hours after the last exposure, blood samples were obtained and all animals were killed. Lung microscopy was performed on 3 animals from each group. Elevated maleic anhydride-specific IgG was found in the group exposed to and challenged with maleic anhydride.

In a second study, two groups of 10 male rats were exposed to maleic anhydride as a particulate aerosol at a target concentration of 500 microgram/m<sup>3</sup>, 6 hours/day for 5 days followed by a three-week rest period. One of the exposed groups then received a 6 hour challenge exposure to a concentration of 317 microgram/m<sup>3</sup> trimellitic anhydride; the other group was not exposed. The design and results of the two experiments are shown in the table.

The lung effects are also described in section 4.2.3.

#### **4.4.2 Oral intake**

Groups of 15 rats of either sex received maleic anhydride in the diet at levels corresponding to 0, 20, 40, 100, 250 or 600 mg/kg b.w./day for 90 days. At 100 mg/kg b.w./day and above, pale enlarged kidneys were found; histopathological changes included nephritis with tubular dilatation, hypertrophy, degeneration and regeneration of tubular epithelial cells. (Dow Chemical Company undated – quoted from HSE 1996).

A follow-up study was conducted, with a group size of 75 in the control group and 50 in the treated groups. The dietary dose levels were 0, 250 or 600 mg/kg b.w./day

and the duration either 90 or 183 days. Again, kidney changes were found, however of greater severity than in the previous study. (Dow Chemical Company 1975b – quoted from HSE 1996).

In a carcinogenicity study groups of 126 rats/sex received dietary doses of 0,10, 32, or 100 mg/kg b.w./day for up to 2 years with interim sacrifices at 6, 12, and 18 months. The only clear treatment-related effect was a slight reduction (6%) in bodyweight gain at the two highest dose levels. Analysis of the diet indicated a lower than intended content of test substance ranging from 44 to 93% of the nominal concentration in the high dose samples. (CIIT 1983 – quoted from HSE 1996).

Groups of 4 dogs/sex received dietary doses of maleic anhydride of 0, 20, 40 or 60 mg/kg b.w./day for 90 days. No clear signs of toxicity were observed. (Monsanto Company 1981 – quoted from HSE 1996).

Table 4. Design of the Amoco 1991 rat studies described in the text

Group	First experiment			Second experiment	
	1 (n= 10 males + 10 females)	2 (n= 10 males + 10 females)	3 (n= 10 males + 10 females)	1 (n=10 males)	2 (n=10 males)
Exposure	maleic anhydride 500 microgram/m <sup>3</sup> 6h/day, 5 d	0	0	maleic anhydride 500 microgram/m <sup>3</sup> 6h/day, 5 d	maleic anhydride 500 microgram/m <sup>3</sup> 6h/day, 5 d
Challenge	maleic anhydride 500 microgram/m <sup>3</sup> 6h	maleic anhydride 500 microgram/m <sup>3</sup> 6h	0	trimellitic anhydride 317 microgram/m <sup>3</sup> 6h	0
Results: Blood level of IgG	Elevated maleic anhydride IgG antibody level	No antibody elevation	No antibody elevation	Elevated maleic anhydride specific antibodies	Elevated maleic anhydride specific antibodies
Results: Lung parameters	Similar macroscopic and microscopic appearance of lungs, lung weight, and lung volume			Elevated numbers of haemorrhagic lung foci in 2 animals	Elevated numbers of haemorrhagic lung foci in 2 animals, microscopic lung lesions in 1 animal

#### 4.4.3 Dermal exposure

No data have been found.

#### 4.5 Toxicity to reproduction

##### 4.5.1 Inhalation

No data have been found.



#### 4.5.2 Oral intake

Groups of 10 male and 10 female rats ( $F_0$ ) generation received 99% pure maleic acid in corn oil by gavage at dose levels of 0, 20, 55, or 150 mg/kg b.w./day. After 80 days' treatment, the  $F_0$  animals were mated to produce an  $F_{1a}$  generation. After the weaning of  $F_{1a}$  pups, the  $F_0$  generation was mated again to produce an  $F_{1b}$  generation. Ten male and 20 female  $F_{1b}$  pups from each group were selected for continued treatment and were mated twice to produce the  $F_{2a}$  and  $F_{2b}$  generations. The study was terminated at weaning of the  $F_{2b}$  generation. At 150 mg/kg b.w./day over half of the  $F_0$  and the majority of the  $F_1$  generation died. Renal cortical necrosis and microscopic bladder calculi were found in a number of animals. At 20 or 55 mg/kg b.w./day, gastric mucosal thickening and inflammation were seen in some parental animals, but no clear systemic toxic effects. A low and variable inter-group pregnancy rate was found (control group 50-70%; low dose group 35-87%). At 150 mg/kg b.w./day,  $F_{1a}$  pup bodyweights were slightly reduced. At 20 or 55 mg/kg b.w./day,  $F_0$  and  $F_1$  pregnancy rate, litter size, incidence of pup abnormalities, pup survival and growth were not affected. No treatment-related histological changes were seen in the  $F_{2b}$  pups. (Monsanto 1982, Short et al. 1986 – both quoted from HSE 1996).

Groups of 25 mated female rats were given 99% pure maleic anhydride in corn oil by gavage from day 6 to 15 of pregnancy at dose levels of 0, 30, 90, or 140 mg/kg b.w./day. Sacrifice and caesarean section took place on day 20. A not statistically significant reduced body weight or body weight gain was found at all dose levels during the first few days of treatment. No effect was found on post-implantation loss, foetal weight, or incidence of foetal variants and major malformations. (Short et al. 1986 – quoted from HSE 1996).

#### 4.5.3 Dermal contact

No data have been found.

### 4.6 Mutagenic and genotoxic effects

#### 4.6.1 *In vitro* studies

The *in vitro* mutagenic and genotoxic effects of maleic anhydride have been studied in bacteria and mammalian cells (Table 5). Maleic anhydride was negative in the Ames test. In the chromosome aberration test, a 16% incidence of aberrations was detected, however, according to HSE (1996), the information given in the publication is not sufficient to validate the apparently positive finding.

#### 4.6.2 *In vivo* studies

An *in vivo* chromosome aberration test has been found (Table 6). The test was negative, but according to HSE (1996), the publication did not contain any evidence that bone marrow cells received adequate exposure. The study is therefore inconclusive.

Table 5. Studies of *in vitro* mutagenic and genotoxic effects

Test system	Procedure	Result	Reference
Ames test. <i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and TA1538	2-500 microgram/plate, toxicity elicited at highest concentration ± metabolic activation	Negative	Monsanto Company (1984 – quoted from HSE 1996)
Ames test. TA98, TA100, TA1535, TA1537	3.3 to 3333 microgram/plate ± metabolic activation, pre-incubation method	Negative	Haworth (1983 – quoted from HSE 1996)
Ames test. TA98, TA100, TA1537	No details given in the review	Negative	Ishidate et al. (1981 – quoted from HSE 1996)
Chromosome aberration test, Chinese hamster lung cells	Up to 125 microgram/ml (no information on toxicity), no metabolic activation, harvest at 24 and 48h, 100 metaphases/dose examined.	Chromosome aberrations (breaks and exchanges) detected in 16% of cells at highest dose level	Ishidate 1988 – quoted from HSE 1996)

Table 6. Studies of *in vivo* mutagenic and genotoxic effects

Test system	Procedure	Result	Reference
Chromosome aberration test, rats	Groups of 15 rats/sex exposed via inhalation for 6 hours to 0, 5, or 165 mg/m <sup>3</sup> maleic anhydride. Sacrifice and bone marrow sampling at 6, 24 and 48 hours	Negative, but see text.	Monsanto Company (1983 – quoted from HSE 1996)

#### 4.7 Carcinogenic effects

In a carcinogenicity study groups of 126 rats/sex received dietary doses of 0, 10, 32, or 100 mg/kg b.w./day for up to 2 years with interim sacrifices at 6, 12, and 18 months. The only clear treatment-related effect was a slight reduction (6%) in bodyweight gain at the two highest dose levels. Analysis of the diet indicated a lower than intended content of test substance ranging from 44 to 93% of the nominal concentration. It was not clear how many animals were available for histopathological examination after 2 years. The tumour incidence was not influenced by treatment. (CIIT 1983 – quoted from HSE 1996).

# 5 Regulations

## 5.1 Ambient air

Denmark (C-value): 0.001 mg/m<sup>3</sup>, Main Group 2 (MST 2002a).

## 5.2 Drinking water

-

## 5.3 Soil

-

## 5.4 Occupational Exposure Limits

Denmark: 0.1 ppm, 0.4 mg/m<sup>3</sup> (At 2005).

ACGIH: 1 mg/m<sup>3</sup> (ACGIH 1999 – quoted from US-EPA 2002).

Germany: 0.1 ppm, 0.4 mg/m<sup>3</sup> (MAK 2005).

## 5.5 EU-classification

Maleic anhydride is classified for acute toxic effects (Xn;R22 – harmful if swallowed), for corrosive effects (C;R34 – causes burns), and for sensitising effects (R42/43 – may cause sensitisation by inhalation and skin contact) (MM 2002b).

## 5.6 IARC

-

## 5.7 US-EPA

Reference dose for chronic oral exposure (RfD) 0.1 mg/kg b.w./day, based on renal lesions observed in a 2-year rat study with a NOAEL of 10 and a LOAEL of 20 mg/kg b.w./day (IRIS 2001).

# 6 Summary and evaluation

## 6.1 Description

Maleic anhydride is a solid substance appearing as colourless needles or white crystalline solid. Maleic anhydride is moderately soluble in water and hydrolyses upon contact with water to malic acid. Maleic anhydride is an intermediate, which is used in a wide range of products, mainly in the manufacture of unsaturated polyester resins.

## 6.2 Environment

Maleic anhydride has not been found in the environment. The substance will hydrolyse with moisture in air or soil.

## 6.3 Human exposure

No data have been found for the general population.

## 6.4 Toxicokinetics

Very little information is available. The occurrence of toxic effects following inhalation or oral exposure, and plasma measurements in dogs orally exposed, indicates that absorption takes place. The acute toxic potency of maleic anhydride after dermal exposure is lower than after oral exposure, indicating that absorption occurs, but to a more limited extent than following oral exposure. No data have been found on distribution, formation of metabolites, or elimination. The occurrence of kidney toxicity in some studies indicates that maleic anhydride reaches this organ and possibly may be eliminated via urine. Since maleic anhydride is easily hydrated to maleic acid, maleic acid may be a metabolite.

## 6.5 Human toxicity

Maleic anhydride is irritating to skin in humans. Severe skin burns and itching have been reported following dermal contact. Dust or vapour has been reported to cause conjunctivitis, inflammation and swelling of the eyelids, severe lachrymation and photophobia. Case reports of respiratory irritation, and feelings of nasal irritation and pulmonary discomfort in a volunteer study indicate that maleic anhydride is a respiratory irritant. In the volunteer study, impairment of smell was also reported. A single worker showed a positive skin reaction to a patch test, indicating that skin sensitisation was present.

Repeated exposure of workers is associated with asthma as evidenced by a number of case reports. It is not known if the asthma has an immunological background. However, maleic anhydride is classified for respiratory sensitisation in the EU. Maleic acid is strongly reactive and structurally related to other chemicals, which cause respiratory sensitisation.

No data regarding toxicity to reproduction, mutagenic and genotoxic effects, and carcinogenic effects have been found.

## 6.6 Animal toxicity

### 6.6.1 Single dose toxicity

Inhalation exposure for 6 hours to up to 199 mg/m<sup>3</sup> of maleic anhydride vapour did not cause mortality in rats. At the highest concentration, signs of eye and nose irritation were observed. Maleic anhydride is moderately toxic by the oral route with a lowest reported LD<sub>50</sub>-value of 235 mg/kg. Maleic anhydride also causes toxicity via the dermal route, however to a low degree, with a reported LD<sub>50</sub>-value of 2620 mg/kg.

### 6.6.2 Irritation

Direct contact with maleic anhydride powder caused severe skin irritation in rabbits, and a 1% solution was highly irritating to the eyes in rabbits.

### 6.6.3 Sensitisation

No relevant studies for skin or respiratory sensitisation have been found.

### 6.6.4 Repeated dose toxicity

The principal effects identified in four-week and six-month inhalation studies in rats, hamsters, and Rhesus monkeys were lesions in the respiratory tract including the nose, trachea and lungs. Clear clinical signs during exposure included nasal discharge and nose bleeding, and respiratory distress. The LOAEC was 1.1 mg/m<sup>3</sup>, which was the lowest concentration tested. No effects in other organs have been described, and the only general toxic effect appears to be reduced body weight gain, or reduction in body weight. Respiratory irritation (elevated numbers of haemorrhagic lung foci) has been demonstrated in a five-day study in rats exposed to a particulate aerosol at 500 microgram/m<sup>3</sup>. However, this study is of limited value because no unexposed group was available for comparison.

In two rat studies (90 days or 90 and 183 days), dietary administration of maleic anhydride resulted in nephritis. The NOAEL was 40 mg/kg b.w./day and the LOAEL 100 mg/kg b.w./day. Renal cortical necrosis was also found in parental animals in a two-generation study at 150 mg/kg b.w./day. However, in a two-year dietary rat study, no kidney effects were reported at this dose level, and the only effect found was reduced body weight gain. In a 90-day dog study with dietary doses up to 60 mg/kg b.w./day no clear toxic signs were observed.

### 6.6.5 Toxicity to reproduction

In a two-generation rat study with gavage administration, no effects on fertility were found, however the pregnancy rate of the control group was exceptionally low (50-70%). The only developmental effect seen was a slight reduction in body-weight of pups from the first litter of the first generation, at this dose level (150

mg/kg b.w./day) severe toxicity including mortality was found in the parental animals.

No effects on foetal development were found in a prenatal toxicity gavage study.

#### **6.6.6 Mutagenic and genotoxic effects**

Maleic anhydride was negative in the Ames test. An in vitro chromosome aberration test showed a positive effect, which however is uncertain. An in vivo chromosome aberration test was negative, but is regarded as inconclusive because of lack of information about bone marrow exposure.

#### **6.6.7 Carcinogenic effects**

No treatment-related differences in tumour incidence were found in a dietary carcinogenicity study in rats.

### **6.7 Critical effect and NOAEL**

The critical effects of maleic anhydride in relation to exposure of humans via air are the effects observed in the respiratory tract including asthma observed following occupational exposure to maleic anhydride. It cannot be excluded that the immune system is involved in the asthma reaction.

Human data are available. According to data in IUCLID (2002), exposure to a concentration of 6-8 mg/m<sup>3</sup> resulted in nasal irritation within 1 minute; among workers repeatedly exposed to 5-10 mg/m<sup>3</sup>, ulceration of nasal mucous membrane, chronic bronchitis and in some cases asthma occurred. It is not known whether the asthma has an allergic background. A NOAEC in humans has not been reported in IUCLID.

In an exposure chamber study with volunteers, concentrations ranging between 22 and 270 mg/m<sup>3</sup> were tested. At the lower range, only very occasional pulmonary discomfort and impairment of smell was registered. This result is not in agreement with the IUCLID data, from which it can be inferred that concentrations in the range 22-270 mg/m<sup>3</sup> would be intolerable. The volunteer study is therefore not regarded as reliable.

In repeated dose inhalation studies in animals, the LOAEC for lesions in the nose (hyperplasia, metaplasia, inflammation) was 1.1 mg/m<sup>3</sup>, and no NOAEC was identified. At higher concentrations, lung squamous metaplasia and intraalveolar haemorrhage has been found. A study indicating lung effects at lower concentrations is regarded as insufficient because of lack of a control group.

The animal LOAEC for respiratory lesions of 1.1 mg/m<sup>3</sup> will be used for the derivation of a quality criterion.

## 7 Quality criterion in air

The quality criterion in air  $QC_{\text{air}}$  is calculated based on a LOAEC of  $1.1 \text{ mg/m}^3$  observed for respiratory lesions in laboratory animals:

$$\begin{aligned} QC_{\text{air}} &= \frac{\text{LOAEC}}{UF_{\text{I}} * UF_{\text{II}} * UF_{\text{III}}} = \frac{1.1 \text{ mg/m}^3}{10 * 10 * 50} \\ &= 0.0002 \text{ mg/m}^3 \end{aligned}$$

The uncertainty factor  $UF_{\text{I}}$  accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The  $UF_{\text{II}}$  accounting for intra-species variability is set to 10 reflecting the range in biological sensitivity within the human population. The  $UF_{\text{III}}$  is set to 50 because an effect level has been used instead of a NOAEC, and because there is concern for respiratory allergy.

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## **Evaluation of health hazards by exposure to Maleic anhydride and proposal of a health-based quality criterion for ambient air**

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to Maleic anhydride. This resulted in 2006 in the present report which includes a health-based quality criterion for the substance in ambient air.



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