CHRONIC TOXICITY SUMMARY

MALEIC ANHYDRIDE

(2,5-furandione; cis-butenedioic anhydride; toxilic anhydride; maleic andride)

CAS Registry Number: 108-31-6

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.7 µg/m^3** (2.5 ppb**)**
Critical effect(s)	Neutrophilic infiltration of the nasal epithelium; irritation of the respiratory system in rats, hamsters and monkeys
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1995)

Description	Colorless or white solid
Molecular formula	$C_4H_2O_3$
Molecular weight	98.06 g/mol
Boiling point	202°C
Melting point	52.8°C
Vapor pressure	0.1 torr @ 25°C (AIHA, 1970)
Solubility	Soluble in water, ether, acetate, chloroform, dioxane; @ 25°C, 227 g/100 g acetone, 112 g/100 g ethyl acetate, 52.5 g/100 g chloroform, 50 g/100 g benzene, 23.4 g/100 g toluene, 19.4 g/100 g o-xylene, 0.6 g/100 g CCl_4, 0.25 g/100 g ligroin
Conversion factor	4.0 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Maleic anhydride is used as a chemical intermediate in the synthesis of fumaric and tartaric acid, certain agricultural chemicals, resins in numerous products, dye intermediates, and pharmaceuticals (HSDB, 1995). It is also used as a co-monomer for unsaturated polyester resins, an ingredient in bonding agents used to manufacture plywood, a corrosion inhibitor, and a preservative in oils and fats. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 7366 pounds of maleic anhydride (CARB, 2000).

IV. Effects of Human Exposure

In many occupational situations workers are exposed to mixtures of acid anhydrides, including maleic anhydride, phthalic anhydride, and trimellitic anhydride. For example, Barker *et al.* (1998) studied a cohort of 506 workers exposed to these anhydrides. In one factory, workers were exposed only to trimellitic anhydride, which has the lowest acceptable occupational exposure limit (40 $\mu g/m^3$) of the three anhydrides. In that factory there was an increased prevalence of sensitization to acid anhydride and work related respiratory symptoms with increasing full shift exposure even extending down to levels below the current occupational standard. However, none of the workplaces had exposure only to maleic anhydride and a dose-response relationship was not seen with mixed exposures.

The following reports involve exposure only to maleic anhydride.

There are several case reports describing asthmatic responses possibly resulting from exposure to maleic anhydride. An individual showed an acute asthmatic reaction after exposure to dust containing maleic anhydride (Lee *et al.*, 1991). Workplace concentrations of maleic anhydride were 0.83 mg/m^3 in the inspirable particulate mass and 0.17 mg/m^3 in the respirable particulate mass. Bronchial provocation testing was performed with phthalic anhydride, lactose, and maleic anhydride. Exposure of this individual to maleic anhydride (by bronchial provocation testing) at 0.83 mg/m^3 and 0.09 mg/m^3 in inspirable and respirable particulate mass, respectively, showed a response of cough, rhinitis, and tearing within two minutes. Within 30 minutes, rales developed in both lungs and peak flow rate decreased 55%.

An individual occupationally exposed to maleic anhydride developed wheezing and dyspnea upon exposure (Gannon *et al.*, 1992). After a period without exposure, two re-exposures both resulted in episodes of severe hemolytic anemia. There was no evidence of pulmonary hemorrhage. Radioallergosorbent testing showed specific IgE antibodies against human serum albumin conjugates with maleic anhydride, phthalic anhydride, and trimellitic anhydride, but not with tetrachlorphthalic anhydride. A critique of the Gannon *et al.* (1992) study by Jackson and Jones (1993) questions the relationship of maleic anhydride exposure to the onset of the anemia, since there were extended periods of exposure to maleic anhydride before symptoms appeared.

Another case report described occupational asthma due to exposure to maleic anhydride (Guerin *et al.*, 1980).

Humans exposed to maleic anhydride showed respiratory tract and eye irritation at concentrations of 0.25 to 0.38 ppm (1 to 1.6 mg/m^3) maleic anhydride (Grigor'eva, 1964). No irritation was reported at 0.22 ppm maleic anhydride.

V. Effects of Animal Exposure

Short *et al.* (1988) chronically exposed CD rats (15/sex/group), Engle hamsters (15/sex/group), and rhesus monkeys (3/sex/group) to maleic anhydride by inhalation. Four groups of each species were exposed to concentrations of 0, 1.1, 3.3, or 9.8 mg/m^3 maleic anhydride for 6

hours/day, 5 days/week, for 6 months in stainless steel and glass inhalation chambers. Solid maleic anhydride was heated to 53°C to generate vapors, which were then mixed with a stream of nitrogen. Chamber target levels were monitored by gas chromatography as total maleic (maleic anhydride plus maleic acid). No exposure-related increase in mortality occurred. Of the species examined, only rats showed significant changes in body weight during the course of the experiment, with reductions among males in the high-dose groups after exposure day 40 and a transient weight reduction from days 78-127 in the mid-dose group. All species exposed to any level of maleic anhydride showed signs of irritation of the nose and eyes, with nasal discharge, dyspnea, and sneezing reported frequently. No exposure-related eye abnormalities were reported. The severity of symptoms was reported to increase with increased dose. No dose-related effects were observed in hematological parameters, clinical chemistry, or urinalysis. No effects on pulmonary function in monkeys were observed. Dose-related increases in the incidence of hyperplastic change in the nasal epithelium occurred in rats in all exposed groups, and in hamsters in the mid- and high-dose groups. Neutrophilic infiltration of the epithelium of the nasal tissue was observed in all species examined at all exposure levels. All changes in the nasal tissues were judged to be reversible. The only other significant histopathological observation was slight hemosiderin pigmentation in the spleens of female rats in the high-dose group.

Incidence of epithelial hyperplasia of the nasal mucosa in animals from Short *et al*. (1988)

Maleic anhydride (mg/m^3)	0	0	1.1	1.1	3.3	3.3	9.8	9.8
Pathology grade	Trace	Mild	Trace	Mild	Trace	Mild	Trace	Mild
Rat								
Male	0/15	0/15	2/15	6/15	1/15	14/15	0/15	12/15
Female	0/15	0/15	6/15	5/15	4/15	10/15	0/15	14/15
Combined		0/30		11/30		24/30		26/30
Hamster								
Male	0/15	0/15	0/15	0/15	0/15	5/15	0/15	8/15
Female	0/15	0/15	0/15	0/15	4/15	4/15	1/15	4/15
Combined		0/30		0/30		9/30		12/30
Monkey								
Male	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Female	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Combined		0/6		0/6		0/6		0/6

The teratogenicity and multigeneration reproductive toxicity of maleic anhydride were also investigated (Short *et al.*, 1986). To evaluate teratogenicity, pregnant CD rats were treated orally with maleic anhydride in corn oil at concentrations of 0, 30, 90, or 140 mg/kg-day from gestational days 6-15. Animals were necropsied on gestational day 20. No statistically significant dose-related effects were observed in maternal weight gain, implantation, fetal viability, post-implantation loss, fetal weight, or malformations. Groups of 10 male rats and 20 female rats/group (F_0 animals) were orally treated with 0, 20, 55, or 150 mg/kg-day maleic anhydride in corn oil to study multigeneration reproductive toxicity. Animals within the same dose group were bred together after 80 days of treatment to produce two F_1 generation animals (F_{1a} and F_{1b}) and animals from the F_1 generation were interbred to produce two F_2 generation animals (F_{2a} and F_{2b}). A significant increase in mortality was observed among both F_0 and F_1

generation animals in the high-dose group. Total body weight was significantly reduced in animals in the high-dose group at Week 11 of exposure for the F_0 generation males and females and at Week 30 of exposure in the F_1 generation males. No consistent pattern of dose- or treatment-related effect on fertility, litter size, or pup survival was observed. Examination of F_0 animals showed necrosis of the renal cortex in the high-dose group (60% of males and 15% of females). Absolute kidney weights were significantly increased in F_1 females in the low- and mid-dose groups, although there was no histological correlate. No changes in organ weight or histology were observed in the F_2 generation animals.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Short *et al.*, 1988
Study population	Rats (15/sex/group), hamsters (15/sex/group), monkeys (3/sex/group)
Exposure method	Discontinuous inhalation exposure (0, 1.1, 3.3, or 9.8 mg/m^3)
Critical effects	Neutrophilic infiltration of the nasal epithelium; epithelial hyperplasia; respiratory irritation
LOAEL	1.1 mg/m^3
NOAEL	Not observed in rats
BMC_{05}	0.12 mg/m^3 for mild epithelial hyperplasia in rats (males and females combined)
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	6 months
Average experimental exposure	21 µg/m^3 for the BMC_{05} (0.12 x 6/24 x 5/7 x 1000)
Human equivalent concentration	21 µg/m^3 for the BMC_{05} (Due to the lack of aerosol particle size data for the critical study, a human equivalent concentration could not be developed using recommended methods of inhalation dosimetry.)
LOAEL uncertainty factor	not needed in benchmark approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3 (see below)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.7 µg/m^3 0.2 ppb)

Short *et al.* (1988) examined the toxicity of maleic anhydride to rats, hamsters, and monkeys by the inhalation route of exposure. Dose- and exposure related effects, although mild and reversible, were observed at all exposure levels. Specifically, exposure to maleic anhydride vapors resulted in hyperplastic change in the nasal epithelium of rats and hamsters (obligate nose breathers). Neutrophilic infiltration of the nasal epithelium was observed in all three species at all levels of exposure. All species also showed signs of irritation at all exposure levels. The observation that acute maleic anhydride is a strong respiratory irritant to humans (ACGIH, 1992)

suggests that this is a valid endpoint of toxicity to humans as well. Human exposure at levels as low as ~1 mg/m^3 appears to trigger acute asthmatic reactions in sensitive individuals (Lee *et al.*, 1991). The histological changes observed by Short *et al*. occurring as a result of inhalation exposure to a known strong irritant such as maleic anhydride are considered to be the adverse effect of repetitive acute exposures, rather than a chronic response, in the development of the REL.

The chronic REL was developed using the benchmark approach. The gamma model in the U.S. EPA's BMDS software yielded a BMC_{05} of 0.12 mg/m3 for mild epithelial hyperplasia in male and female rats combined. Because of the similarities among species and the inclusion of monkeys in the study, an interspecies uncertainty factor of 3, rather than 10, was used. Although there is no evidence of a toxic response similar to the development of asthma in animals, the 1.1 mg/m^3 LOAEL from the animal studies of Short *et al.* (1988) results in a REL of 0.7 $\mu g/m^3$ which should protect asthmatics from maleic and other anhydrides.

VII. Data Strengths and Limitations for Development of the REL

The major strengths of the REL for maleic anhydride are the availability of multiple-species, multiple-dose subchronic inhalation studies, and the observation of a mild effect LOAEL. The major uncertainties are the lack of human data and the lack of a NOAEL observation.

VIII. Potential for Differential Impacts on Children's Health

Minimal teratogenic and reproductive adverse effects were seen at the lowest oral dose of maleic anhydride (20 mg/kg-day), given to rats during gestation (Short et al., 1986). This dose is equivalent to a person inhaling 70 mg/m^3. Thus the chronic REL of 0.7 $\mu g/m^3$ should protect children. Maleic anhydride is a respiratory irritant and an inducer of asthma. Exacerbation of asthma has a more severe impact on children than on adults. However, there is no direct evidence in the literature to quantify a differential effect of maleic anhydride in children.

IX. References

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