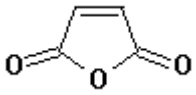
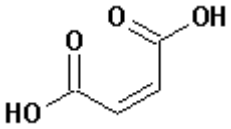
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-31-6 110-16-7
Chemical Name	Maleic Anhydride Maleic Acid
Structural Formula	Maleic Anhydride: $C_4H_2O_3$  Maleic Acid: $C_4H_4O_4$ 

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

Maleic anhydride is readily hydrolyzed to maleic acid under aqueous conditions. As a result, these two chemicals are presented because of the conditions used to test their toxicity. The only difference may be due to the potential for maleic anhydride to form haptens by acylating with amino acids, resulting in an immunological response (dermal and respiratory sensitization).

Human Health

Maleic anhydride and maleic acid exhibit relatively low acute toxicity by the oral and dermal routes, with the oral LD_{50} of about 1.0 g/kg in rats and an acute dermal LD_{50} in the range of 1.6 to 2.6 g/kg in rabbits. Maleic anhydride and maleic acid have been reported to be severely irritating to the skin and eyes of rabbits. Maleic anhydride has been shown to be a skin sensitizer to guinea pigs and a possible respiratory sensitizer to rats. There have been a few published human cases suggesting that maleic anhydride provokes asthma in a relatively small proportion of exposed workers; however, questions have been raised about whether the asthma was related to maleic anhydride exposure. Although no sensitization data exist for maleic acid, it is not predicted to be either a skin or respiratory sensitizer.

Repeated exposure of maleic anhydride by inhalation to rats, hamsters, and monkeys have resulted in effects that were limited to the respiratory tract and eye irritation. In a four-week study, rats exposed six hours/day to 0, 12, 32, and 84 mg/m^3 (0, 3, 8, 21 ppm) maleic anhydride showed evidence of nasal, trachea, and lung irritation at all exposure levels. These effects were concentration-related and included epithelial hyperplasia and the presence of inflammatory exudates in the nasal turbinates and trachea; and epithelia hyperplasia, squamous metaplasia, and intra-alveolar hemorrhage in the lung. Increased incidence of hemorrhagic lung foci were also observed in the 32 and 86 mg/m^3 exposed groups. The LOAEL was 12 mg/m^3 (3 ppm). In a six-month inhalation study in which rats, hamsters, and monkeys were exposed to 0, 1.1, 3.3, or 9.8 mg/m^3 (0, 0.3, 0.8, or 2.4 ppm), respiratory tract and eye irritation were observed in rats and hamsters exposed to 3.3 or 9.8 mg/m^3 (0.8 or 2.4 ppm) and monkeys to 9.8 mg/m^3 (2.4 ppm),

with body weight reductions only in male rats from the high-exposure group at study termination. Hyperplastic changes in the nasal tissues, which ranged in severity from trace to mild, were present in rats at all exposure levels and in hamsters in the mid- and high-exposure levels. Metaplastic changes in the nasal tissues occurred in both rats and hamsters at all exposure levels. Both the hyperplastic and metaplastic changes in the nasal passages are considered indicative of irritation and judged to be reversible. The NOAEL for rats is 3.3 mg/m^3 (0.8 ppm) and the NOAEL for hamsters and monkeys is 9.8 mg/m^3 (2.4 ppm). Oral feeding studies with maleic anhydride have resulted in kidney damage in rats at relatively high doses ($\geq$ 100 mg/kg/day after 90 days of exposure), with the effects being more severe in males than in females. The effects appear to be largely in the tubular cells, with some effects also occurring in the glomeruli. The kidney effects are likely due to maleic acid, since maleic anhydride rapidly hydrolyzes to maleic acid under aqueous conditions and maleic acid is known to cause kidney damage with the target site being tubular cells. However, no kidney effects were observed in rats that were fed diets containing 32 and 100 mg/kg/day maleic anhydride for two years. A dietary study in dogs dosed at 0, 20, 40, or 60 mg/kg maleic anhydride, seven days a week for 90 days, showed no adverse effects related to maleic anhydride exposure, except for decreased food intake for the first few weeks in the high-dose group.

Maleic anhydride and maleic acid were both negative in bacterial gene mutation tests. A single in vitro chromosomal aberration test with and without S-9 was positive for maleic anhydride. Because there is inadequate documentation on this study, it is unclear whether the results were due to maleic anhydride or to a change in pH due to the acidic environment from the hydrolysis of maleic anhydride to maleic acid. Maleic anhydride was negative in an in vivo rat bone marrow chromosomal aberration test. Both maleic anhydride and maleic acid were not carcinogenic when given to rats in their diets for two years up to doses of 100 mg/kg/day.

In a two-generation reproductive toxicity study, rats were dosed via gavage to 0, 20, 55 and 150 mg/kg/day maleic anhydride. The NOAEL for reproductive effects is 55 mg/kg/day (highest dose tested due to parental death at 150 mg/kg/day.) However, in the parental group adverse effects (mortality, body weight changes, and respiratory irritation) were observed at 150 mg/kg/day (the highest dose tested.) In addition, there were histopathological effects in the kidneys and bladder of the parental animals (first generation only) in all treated dose groups. The LOAEL for parental effects is 20 mg/kg/day. No developmental toxicity was observed when pregnant rats were dosed with maleic anhydride via gavage to 0, 30, 90 and 140 mg/kg/day. The dams in all dose groups either lost weight or failed to gain weight between days 6 and 9 of gestation; however, this effect was not statistically significant at any interval and was reversible. As a result, the NOAEL (maternal) was determined to be 140 mg/kg/day. Negative results for reproductive and developmental toxicity of maleic acid are inferred from the rapid hydrolysis of maleic anhydride to maleic acid.

There have been been a few published human cases suggesting that maleic anhydride provokes asthma in a relatively small proportion of exposed workers. Questions, however, have been raised whether the asthma was actually related to maleic anhydride exposure.

Environment

Maleic anhydride has a melting point of 51.2 to 53.1 ^{0}C, a boiling point of 185 ^{0}C, and vapour pressures of 15.1, 37.7, and 108 Pa at 22, 30, and 40 ^{0}C, respectively. The log K_{ow} of maleic anhydride (as maleic acid) is –2.61. The water solubility of maleic anhydride (as maleic acid) was ~400 g/L at 20^{o}C.
Maleic acid has a melting point of 130-144 ^{0}C. This range is based on three entries under different conditions: 138-139 ^{o}C when crystallized from water; 130-135 ^{o}C when crystallized from alcohol, and 144^{o}C in air. The boiling point has been reported to be about 138 ^{0}C, at temperature at which decomposition occurs. This temperature is known to result in isomerization to fumaric acid. The vapor pressure of maleic acid is reported to be 4.8 x 10^{-3} Pa at 25 ^{0}C. The dissociation contants for maleic acid are at 25 ^{o}C: K_1: 1.14 x 10^{-2} (pH = 1.94) and K_2: 5.95 x 10^{-7} (pH = 6.22).

Maleic anhydride and maleic acid are not persistent in the environment and are not expected to bioaccumulate in food webs. In the presence of water, maleic anhydride rapidly hydrolyzes to form maleic acid. The half-life of the hydrolysis of maleic anhydride to maleic acid in water at 25^{o}C has been determined to be approximately 22 seconds. The half-life of maleic anhydride in air is estimated to be 4.2 to 18.6 hours (the estimated rate constants range from 4.3 x 10^{-11} to 4.9 x 10^{-17} cm^3 $molecule^{-1}$ sec^{-1}), due primarily to direct reactions with photochemically generated hydroxyl radicals. For maleic acid, the half-life in air is estimated to be 1.346 and 1.205 days for the cis- and trans-

isomers, respectively.

Maleic anhydride and maleic acid are readily biodegraded under aerobic conditions in sewage sludge, and are expected to biodegrade in soil and water as well. Fugacity-based fate and transport modelling suggest that maleic anhydride, hydrolyzed to maleic acid in water and under humid conditions, will partition primarily to water. Level III fugacity modelling indicates water as the primary compartment for distribution (air 0.3%, water 59%, soil 40.6%, sediment 0.02%).

Acute aquatic toxicity testing indicates a low order of toxicity when the effect of pH is taken into consideration. Acute values were 96-hour LC_{50} in fish – 75 mg/Land 48-hour EC_{50} in daphnids – 330 mg/L. (in non-neutralized conditions, pH 2-3). In a study which took pH into consideration, the 24-hour daphnid EC_{50} was 88, 83, and 5600 mg/liter for non-neutralized maleic anhydride, non-neutralized maleic acid, and neutralized maleic anhydride, respectively. This supports the observation that pH may be a significant confounder in the observed aquatic toxicity of maleic anhydride/maleic acid.

The 72-hour algae NOEC of 130 mg/L (measured as maleic acid in neutralized conditions and the highest dose tested). The combination of low aquatic toxicity, low log P_{ow} and readily biodegradability suggest no significant hazard of long-term effects in the aquatic environment.

Exposure

In the United States, the capacity for maleic anhydride was 590 million pounds (267,565 metric tonnes) in 1999. Maleic anhydride is produced from the oxidation of butane using fixed-bed or fluid-bed processes. It can also be generated through the oxidation of benzene. Most of the maleic anhydride produced is used in unsaturated polyester resins, while smaller amounts are used in the production of fumaric and malic acid; lube oil additives, maleic copolymers, agricultural chemicals, and 1-4-butanediol. Maleic acid is an intermediate in the production of maleic anhydride. It is recovered in the manufacturing process to be used as a feedstock for tetrahydrofuran, fumaric acid, and 1,4-butanediol. Occupational exposure to maleic anhydride and maleic acid is likely to occur by inhalation and dermal routes in settings where maleic anhydride is produced or used. Maleic anhydride itself has no known consumer uses. Because maleic anhydride is rapidly hydrolyzed to form maleic acid in the presence of water, consumer and environmental exposures to maleic anhydride are not anticipated. Data regarding these potential exposures to maleic acid are lacking, but exposures are expected to be low outside of the workplace.

RECOMMENDATION

These chemicals are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

These chemicals possess properties indicating a hazard for human health (maleic anhydride is a skin/eye irritant, a skin - and possibly respiratory - sensitizer and causes minor effects at low doses in repeated-dose toxicity tests). Based on data presented by the Sponsor country, exposure is anticipated to be low to humans (controlled in occupational settings and no known exposures to consumers) and therefore these chemicals are currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by Sponsor countries.

Environment:

These chemicals are currently of low priority for further work because of their low hazard profile.

Note:
In the US maleic anhydride is listed in a proposed rule by the U.S. EPA Office of Air and Radiation, Hazardous Air Pollutants (HAPs), Title 1 Section 112.