Maleic anhydride; CASRN 108-31-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Maleic anhydride

File First On-Line 08/22/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	08/22/1988
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Maleic anhydride
CASRN — 108-31-6
Last Revised — 08/22/1988

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
No adverse effects **Rat Oral Chronic Study** **U.S. EPA, 1983**	NOAEL: 10 mg/kg/day	100	1	1E-1 mg/kg/day
Renal lesions **Rat Oral Multigeneration Reproduction Study** **U.S. EPA, 1982**	LOAEL: 20 mg/kg/day			

*Conversion Factors -- Actual dose tested

I.A.2. Principal and Supporting Studies (Oral RfD)

U.S. EPA. 1983. Chronic Dietary Administration of Maleic Anhydride. Vol. 1: Narrative. Microfiche No. OTS 1283-0277. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

U.S. EPA. 1982. Three-generation reproduction study in rats (modified to a 2-generation study). Microfiche No. OTS 0206655. Document ID 878214777. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

U.S. EPA (1983) fed groups of 30 male and 30 female Fischer 344 rats dietary maleic anhydride at levels which provided intakes of 10, 32, or 100 mg/kg/day for 2 years. The parameters of toxicity assessed were general appearance and behavior, body and organ weights, food

consumption, hematology, urinalysis, clinical chemistry, mortality, and gross and comprehensive histological examination. At 32 and 100 mg/kg/day, male rats had slight but insignificant decrease in body weight. A marginal decrease in body weight was also observed in female rats at 32 and 100 mg/kg/day. No other adverse effects attributable to exposure to maleic anhydride were noted at any treatment level.

U.S. EPA (1982) conducted a multigeneration reproduction study using CD rats. Groups of 10 male and 20 female rats were given maleic anhydride in corn oil by gavage at 0, 20, 55, or 150 mg/kg/day until sacrifice. Compound-related mortality and renal pathological changes occurred in F0 and F1 parent rats at 150 mg/kg/day. In rats surviving until sacrifice, multiple renal lesions occurred in F0 rats treated at 20, 55, and 150 mg/kg/day and were considered dose-related.

It appears from the studies described previously that maleic anhydride is more toxic when administered by gavage than feed. Observed differences in toxicity may therefore be attributable to the route of administration.

Thus, 20 mg/kg/day in the multigeneration study is the LOAEL and 10 mg/kg/day in the 2-year study is the NOAEL for chronic oral exposure.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — 10 for species-to-species extrapolation and 10 to protect sensitive humans.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

90-Day Feeding Study - rat: doses 0, 20, 40, 100, 250 or 600 mg/kg/day; LOAEL is 100 mg/kg/day for gross and histopathological renal lesions and NOAEL is 40 mg/kg/day (U.S. EPA, 1975a).

183-Day Feeding Study - rat: doses 0, 250 and 600 mg/kg/day; LOAEL is 250 mg/kg/day for renal lesions and increased liver and kidney weights (U.S. EPA, 1977).

90-Day Feeding Study - dog: doses 0, 20, 40 or 60 mg/kg/day; LOAEL is 60 mg/kg/day for hematological effects and the NOAEL is 40 mg.kg.day (U.S. EPA, 1975b).

Reproductive study - rat: doses 0, 30, 90 and 140 mg/kg/day during days 6-15 of gestation; NOAEL is 140 mg/kg/day (U.S. EPA, 1979).

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The level of confidence in the study is medium. The study was conducted by a relevant route of administration at several levels and several endpoints of toxicity were examined. The confidence level in the database is medium since adequately defined NOAELs and LOAELs and reproductive and teratogenic effects data were available. The confidence level in the RfD is medium to reflect the levels of confidence in the studies and database.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 1986

Limited peer review and extensive Agency-wide review, 1986.

ECAO Internal Review, January 1988.

Other EPA Documentation — U.S. EPA, 1975a,b, 1977, 1979, 1982, 1983

Agency Work Group Review — 02/24/1988, 03/24/1988

Verification Date — 03/24/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Maleic anhydride conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Maleic anhydride
CASRN — 108-31-6

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Maleic anhydride
CASRN — 108-31-6

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Maleic anhydride
CASRN — 108-31-6

VI.A. Oral RfD References

U.S. EPA. 1975a. Maleic anhydride. Results of a 90-day dietary feeding study in rats. Microfiche No. OTS 0206649. Document ID 878214746. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

U.S. EPA. 1975b. 90-Day dietary feeding studies on maleic anhydride in beagle dogs. Microfiche No. OTS 0206649. Document ID 878214747. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

U.S. EPA. 1977. A supplemental toxicological study of maleic anhydride incorporated in the diet of male rats for 183 days. Microfiche No. OTS 0206649. Document ID 878214747. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

U.S. EPA. 1979. Four-week inhalation study in rats (IRD-77-108). Microfiche No. OTS 0206655. Document ID 87821477. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

U.S. EPA. 1982. Three-generation reproduction study in rats (modified to a 2-generation study). Microfiche No. OTS 0206655. Document ID 878214777. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

U.S. EPA. 1983. Chronic Dietary Administration of Maleic Anhydride. Vol. 1: Narrative. Microfiche No. OTS 1283-0277. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

U.S. EPA. 1986. Health and Environmental Effects Profile on Maleic Anhydride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC. EPA/600/x-86/196.

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Maleic anhydride
CASRN — 108-31-6

Date	Section	Description
08/22/1988	I.A.	Oral RfD summary on-line
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Maleic anhydride
CASRN — 108-31-6
Last Revised — 08/22/1988

- 108-31-6
- butenedioic anhydride, cis-
- cis-butenedioic anhydride
- 2,5-furandione
- maleic acid anhydride
- Maleic anhydride
- toxilic anhydride