

Phthalic anhydride; CASRN 85-44-9

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 Phthalic anhydride

File First On-Line 09/07/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/07/1988
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 — Phthalic anhydride

CASRN — 85-44-9

Last Revised — 09/07/1988

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
Lung and kidney histopathology	NOAEL: None	1000	1	2E+0 mg/kg/day
Chronic Mouse Oral Study	LOAEL: 12,019 ppm of diet converted to 1562 mg/kg/day			
NCI, 1979				

*Conversion Factors: mouse food consumption = 13% bw/day

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

NCI (National Cancer Institute). 1979. Bioassay of phthalic anhydride for possible carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 159. NTIS PB293594.

B6C3F1 mice, 50/sex/group, were fed diets containing phthalic anhydride for 104 weeks; initial concentrations were 25,000 and 50,000 ppm, but the levels were lowered to 12,500 and 25,000 for males and 6250 and 12,500 ppm for females after 32 weeks because of severe weight loss. The TWA concentrations were 16,346 and 32,692 ppm for the male mice and 12,019 and 24,038 ppm for the female mice. Groups of 20 mice of each sex served as untreated controls. Body weights were measured monthly and comprehensive gross and microscopic examinations were conducted on all animals up to death or sacrifice at termination of experiment. Treatment did not affect survival in either sex of mice, but there was a dose-related inhibition of weight gain; decreases at the end of the study were 12% and 25% in the males and 12% and 27% in the females. Although NCI (1979) concluded that there were no treatment-related nonneoplastic pathological effects in the mice, examination of the incidence data shows significantly increased incidences of lung and kidney lymphocytosis in the low- and high-dose males and females, chronic bile duct inflammation in the high-dose males and females and dose-related adrenal atrophy and mineralization of the thalamus in the low- and high-dose males. Thus, the 12,019 ppm level in female mice is the LOAEL, which when multiplied by a food factor of 0.13 kg

food/kg bw yields a dose of 1562 mg/kg/day. Dividing the LOAEL by an uncertainty factor of 1000 yields a rounded RfD of 2 mg/kg/day, or 109 mg/day for a 70 kg human.

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

UF — 10 for interspecies extrapolation, 10 to protect sensitive subgroups of the human population, and 10 to extrapolate from a LOAEL.

MF — None

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

In the same NCI (1979) study F344 rats (50/sex/group) were fed diets containing 7500 or 15,000 ppm phthalic anhydride for 105 weeks. The mean body weights of the high-dose males were lower than the controls from week 13 to the end of the study, but the decrease was never more than 10%. There were no treatment-related effects on survival or pathology. Phthalic anhydride was reported to be teratogenic in mice following intraperitoneal injection, but teratogenicity or reproductive toxicity has not been studied using the oral route of exposure (Fabro et al., 1982).

I.A.5. Confidence in the Oral RfD

Study — High

Database — Medium

RfD — Medium

Because the NCI (1979) bioassay is a well-designed feeding study in two species that defines a NOAEL and LOAEL, the confidence level is high. Confidence in the database is medium because teratogenicity has not been tested adequately. Confidence in the RfD is rated medium because of the lack of reproductive toxicity data.

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

Source Document — U.S. EPA, 1986

Other EPA Documentation — None

Limited Peer Review and Extensive Agency-wide Review, 1986

Agency Work Group Review — 02/24/1988

Verification Date — 02/24/1988

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 Phthalic anhydride conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to 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 — Phthalic anhydride

CASRN — 85-44-9

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Phthalic anhydride

CASRN — 85-44-9

Not available at this time.

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Phthalic anhydride

CASRN — 85-44-9

VI.A. Oral RfD References

Fabro, S., G. Shull and N.A. Brown. 1982. The relative teratogenic index and teratogenic potency: Proposed components of developmental toxicity risk assessment. *Teratogen. Carcinogen. Mutagen.* 2(1): 61-76.

NCI (National Cancer Institute). 1979. Bioassay of phthalic anhydride for possible carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 159. NTIS PB293594.

U.S. EPA. 1986. Health and Environmental Effects Profile on Phthalic 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.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Phthalic anhydride

CASRN — 85-44-9

Date	Section	Description
09/07/1988	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 — Phthalic anhydride

CASRN — 85-44-9

Last Revised — 09/07/1988

- 85-44-9
- 1,2-benzenedicarboxylic acid anhydride
- 1,3-dihydro-1,3-dioxoisobenzofurandione
- 1,3-phthalandion
- phthalandione
- Phthalic anhydride