# Diethyl phthalate; CASRN 84-66-2

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 Diethyl phthalate

**File First On-Line 09/30/1987**

| Category (section) | Assessment Available? | Last Revised |
|---|---|---|
| **Oral RfD (I.A.)** | yes | 09/30/1987 |
| **Inhalation RfC (I.B.)** | not evaluated | |
| **Carcinogenicity Assessment (II.)** | yes | 09/07/1988 |

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

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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 |
|---|---|---|---|---|
| **Decreased growth rate, food consumption and altered organ weights**<br><br>**Rat, Subchronic Oral Feeding Study**<br><br>**Brown et al., 1978** | NOAEL: 1% of diet (750 mg/kg bw/day)<br><br>LOAEL: 5% of diet (3160 mg/kg bw/day) | 1000 | 1 | 8E-1 mg/kg/day |

* Conversion Factors: Converted doses estimated by principal study authors, based on food consumption and body weight data.

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

Brown, D., K.R. Butterworth, I.F. Gaunt, P. Grasso and S.D. Gangolli. 1978. Short-term oral toxicity study of diethyl phthalate in the rat. Food Cosmet. Toxicol. 16: 415-422.

Groups of CD rats (15/sex) were fed diets containing 0, 0.2, 1.0, or 5.0% DEP for 16 weeks. The authors estimated the mean intakes to be 0, 150, 770, and 3160 mg/kg/day for the males and 0, 150, 750, and 3710 mg/kg/day for the females. Additional groups of five rats/sex were fed similar diets for 2 or 6 weeks. Hematological examinations (red blood cell count, hematocrit, hemoglobin) were performed on animals fed diets for 2, 6, and 16 weeks. Differential white blood cell counts were also conducted on 0 and 5% dose groups at 16 weeks. Food and water intake and body weight were measured for all groups weekly. Urinalyses were conducted during weeks 2, 6, and 15 on 5 to 15 rats/sex/dose group. After 16 weeks of treatment, autopsy, hematologic and histologic examinations were conducted on all animals.

No changes in behavior or other clinical signs of toxicity were observed. The authors reported significantly less weight gain throughout the duration of the experiment in both sexes given 5%

DEP (15 to 25% decrease) and in females (5 to 8% decrease) fed 1% DEP. Mean food consumption of the previous groups was also decreased (by 11 to 23%) relative to controls. No significant dose- or time-related trends in urinalysis or hematology results were found. Absolute weights of brain, heart, spleen, and kidneys were decreased in both sexes fed 5% DEP. Relative weights of the brain, liver, kidneys, stomach, small intestines, and full caecum were significantly greater in both sexes after 16 weeks at the 5% dietary level when compared with controls. No histologic changes because of treatment were reported.

In another experiment summarized by Brown et al. (1978), groups of six rats/sex were pair-fed diets containing either 0 or 5% DEP for 16 weeks. Body weights were measured weekly. The authors reported that rats fed 5% DEP consumed more food and gained less weight than controls. The differences in food consumption (1 to 5%) were not statistically significant, and mean weight differences were 7 to 10%, which the authors reported as statistically significant.

The RfD receives support from the results of a 2-year feeding study using rats (Food Research Laboratories, Inc., 1955). Albino weanling rats (strain not specified) (15/sex) were fed 0, 0.5, 2.5, and 5.0% diethyl phthalate in the diet. Animals were maintained for a 2-year period during which two males and two females/group were examined at 12-week intervals for the following: red and white blood cell counts, differential white count, hemoglobin, blood sugar and nitrogen, and urinalysis. Growth of animals in the 5% treatment group was retarded throughout the study, with no depression of food intake. There was a significant decrease in efficiency of food utilization in this group compared with controls. There were no other treatment-related effects either on the parameters listed above or on gross organ appearance or histopathology.

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

UF — A factor of 10 for extrapolation from subchronic to chronic exposure, 10 for interspecies variation, and an additional 10-fold factor to protect sensitive human subpopulations were used in determining the RfD.

MF — None

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

Data regarding developmental and reproductive effects is extremely limited. Singh et al. (1972) observed skeletal malformations in Sprague-Dawley rats after i.p. administration (0.506, 1.012, and 1.686 mL/kg) on days 5, 10, and 15 of gestation. In addition, fetuses were significantly smaller than untreated controls. Exposure to DEP does not appear to affect the reproductive performance of mice after oral administration of 0.25, 1.25, and 2.5% DEP for 18 weeks (NTP,

1984). Second-generation breeding pairs exposed to 2.5% DEP exhibited increased right epididymis and prostate weights in males and decreased pituitary weight in females (NTP, 1984).

### I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Low
RfD — Low

Sufficient numbers of rats of both sexes were employed and multiple endpoints, including histopathology, were studied; confidence in the study is rated medium. Since only limited supporting data are available and the chosen study was of less than lifetime duration, confidence in the database is rated low. Low confidence in the RfD follows.

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

The RfD Work Group meeting notes of 01/22/1986 directed a review of the Brown et al. (1978) study. The review has resulted in a different evaluation than presented on 01/22/1986.

Agency Work Group Review — 01/22/1986, 07/16/1987

Verification Date — 07/16/1987

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 Diethyl phthalate 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)

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Not available at this time.

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## II. Carcinogenicity Assessment for Lifetime Exposure

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Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

### II.A. Evidence for Human Carcinogenicity

#### II.A.1. Weight-of-Evidence Characterization

Classification — D; not classifiable as a human carcinogen

Basis — Pertinent data regarding carcinogenicity were not located in the available literature.

#### II.A.2. Human Carcinogenicity Data

None.

### II.A.3. Animal Carcinogenicity Data

Inadequate. Dietary studies in rats with exposure durations of 2 years (Food Research Laboratories, Inc., 1955) and 16 weeks (Brown et al., 1978) were not designed to measure carcinogenic effects.

### II.A.4. Supporting Data for Carcinogenicity

DEP was found to be a weak direct-acting mutagen in forward and reverse mutation assays in Salmonella typhimurium (Seed, 1982; Rubin et al., 1979; Kozumbo et al., 1982). DEP was negative in mammalian cell chromosomal aberration assays (Ishidate and Odashima, 1977; Tsuchiya and Hattori, 1977). Research indicates that DEP is hydrolyzed to monoesters (Rowland et al., 1977). There is limited evidence that DEP is a weak inducer of peroxisome proliferation (U.S. EPA, 1987).

## II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

## II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

## II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

### II.D.1. EPA Documentation

Source Document — U.S. EPA, 1987

The 1987 Drinking Water Criteria Document for Phthalic Acid Esters has received OHEA review.

### II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 08/26/1987

Verification Date — 08/26/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Diethyl phthalate 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.

### II.D.3. EPA Contacts (Carcinogenicity Assessment)

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).

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

## VI. Bibliography

Substance Name — Diethyl phthalate
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### VI.A. Oral RfD References

Brown, D., K.R. Butterworth, I.F. Gaunt, P. Grasso and S.D. Gangolli. 1978. Short-term oral toxicity study of diethyl phthalate in the rat. Food Cosmet. Toxicol. 16: 415-422.

Food Research Laboratoes, Inc. 1955. Toxicological studies of diethyl phthalate. Laboratory No. 67567. Celanese Corp. of America. Summit Research Laboraties, Summit, NJ.

NTP (National Toxicology Program). 1984. Diethyl Phthalate: Reproduction and fertility assessment in CD-1 mice when administered in the feed. Final report. NTP, Research Triangle Park, NC.

Singh, A.R., W.H. Lawrence and J. Autian. 1972. Teratogenicity of phthalate esters in rats. J. Pharmacol. Sci. 61(1): 51-55.

## VI.B. Inhalation RfC References

None

## VI.C. Carcinogenicity Assessment References

Brown, D., K.R. Butterworth, I.F. Gaunt, P. Grasso and S.D. Gangolli. 1978. Short-term oral toxicity study of diethyl phthalate in the rat. Food Cosmet. Toxicol. 16: 415-422.

Food Research Laboratories, Inc. 1955. Toxicological studies of diethyl phthalate. Laboratory No. 67567. Celanese Corp. of America. Summit Research Laboratories, Summit, NJ.

Ishidate, M., Jr. and S. Odashima. 1977. Chromosome tests with 134 compounds on Chinese hamster cells in vitro -- A screening test for chemical carcinogens. Mutat. Res. 48: 337-354.

Kozumbo, W.J., R. Kroll and R.J. Rubin. 1982. Assessment of the mutagenicity of phthalate esters. Environ. Health Perspect. 45: 103-109.

Rowland, I.R., R.C. Cottrell and J.C. Phillips. 1977. Hydrolysis of phthalate esters by the gastro-intestinal contents of the rat. Food Cosmet. Toxicol. 15: 17-21.

Rubin, R.J., W. Kozumbo and R. Kroll. 1979. Ames mutagenic assay of a series of phthalic acid esters: Positive response of the dimethyl and diethyl esters in TA100. Soc. Toxicol. Ann. Meet., New Orleans, March 11-15. p. 11. (Abstract)

Seed, J.L. 1982. Mutagenic activity of phthalate esters in bacterial liquid suspension assays. Environ. Health Perspect. 45: 111-114.

Tsuchiya, K. and K. Hattori. 1977. Chromosomal study on human leukocyte cultures treated with phthalic acid ester. Hokkaidoritus Eisei Kenkyusho Ho. 26: 114. (Abstract)

U.S. EPA. 1987. Drinking Water Criteria Document for Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

## VII. Revision History

Substance Name — Diethyl phthalate
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| Date | Section | Description |
|---|---|---|
| **09/07/1988** | II. | Carcinogen summary on-line |
| **12/03/2002** | I.A.6., II.D.2. | Screening-Level Literature Review Findings message has been added. |

## VIII. Synonyms

Substance Name — Diethyl phthalate
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- 84-66-2
- ANOZOL
- 1,2-BENZENEDICARBOXYLIC ACID, DIETHYL ESTER
- Diethyl phthalate
- DPX-F5384
- ESTOL 1550

- ETHYL PHTHALATE
- NCI-C60048
- NEANTINE
- PALATINOL A
- PHTHALOL
- PHTHALSAEUREDIAETHYLESTER
- PLACIDOL E
- RCRA WASTE NUMBER U088