

Di(2-ethylhexyl)phthalate (DEHP); CASRN 117-81-7

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 DEHP

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	01/31/1987
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)

Substance Name — Di(2-ethylhexyl)phthalate (DEHP)
CASRN — 117-81-7
Primary Synonym — Bis(2-ethylhexyl)phthalate
Last Revised — 01/31/1987

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
Increased relative liver weight	NOAEL: none	1000	1	2E-2 mg/kg/day
Guinea Pig Sub-chronic-to-Chronic Oral Bioassay	LOAEL: 0.04% of diet (19 mg/kg bw/day)			
Carpenter et al., 1953				

*Conversion Factors: none

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

Carpenter, C.P., C.S. Weil and H.F. Smyth. 1953. Chronic oral toxicity of di(2-ethylhexyl)phthalate for rats and guinea pigs. Arch. Indust. Hyg. Occup. Med. 8: 219-226.

The following numbers of guinea pigs were fed diets containing DEHP for a period of 1 year: 24 males and 23 females consumed feed containing 0.13% DEHP; 23 males and 23 females consumed feed containing 0.04% DEHP; and 24 males and 22 females were fed the control diet. These dietary levels corresponded to 64 or 19 mg/kg bw/day based on measured food consumption. No treatment-related effects were observed on mortality, body weight, kidney weight, or gross pathology and histopathology of kidney, liver, lung, spleen, or testes. Statistically significant increases in relative liver weights were observed in both groups of treated females (64 and 19 mg/kg bw/day).

Groups of 32 male and 32 female Sherman rats were maintained for 2 years on diets containing either 0.04, 0.13 or 0.4% DEHP (equivalent to 20, 60, and about 195 mg/kg bw/day based on measured food consumption). An F1 group of 80 animals was fed the 0.04% diet for 1 year. Mortality in the F1 treated and control groups was high; 46.2 and 42.7%, respectively, survived

to 1 year. There was, however, no effect of treatment on either parental or F1 group mortality, life expectancy, hematology, or histopathology of organs. Both parental and F1 rats receiving the 0.4% DEHP diet were retarded in growth and had increased kidney and liver weights.

It appears that guinea pigs offer the more sensitive animal model for DEHP toxicity. A LOAEL in this species is determined to be 19 mg/kg/day.

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

UF — Factors of 10 each were used for interspecies variation and for protection of sensitive human subpopulations. An additional factor of 10 was used since the guinea pig exposure was longer than subchronic but less than lifetime, and because, while the RfD is set on a LOAEL, the effect observed was considered to be minimally adverse.

MF — None

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

Dietary levels of 0, 0.01, 0.1, and 0.3% DEHP (greater than 99% pure) were administered to male and female CD-1 mice that were examined for adverse fertility and reproductive effects using a continuous breeding protocol. DEHP was a reproductive toxicant in both sexes significantly decreasing fertility and the proportion of pups born alive per litter at the 0.3% level, and inducing damage to the seminiferous tubules (NTP, 1984). DEHP has been observed to be both fetotoxic and teratogenic (Singhe, 1972; Shiot and Nishimura, 1982).

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — Medium

RfD — Medium

The study by Carpenter et al. (1953) utilized sufficient numbers of guinea pigs and measured multiple endpoints. The fact that there were only two concentrations of DEHP tested precludes a rating higher than medium. Since there are corroborating chronic animal bioassays, the database is likewise rated medium. Medium confidence in the RfD follows.

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

The RfD has been reviewed by the RfD Work Group. Documentation may be found in the meeting notes of 01/22/1986.

Other EPA Documentation — None

Agency Work Group Review — 01/22/1986

Verification Date — 01/22/1986

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 — Di(2-ethylhexyl)phthalate (DEHP)

CASRN — 117-81-7

Primary Synonym — Bis(2-ethylhexyl)phthalate

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Di(2-ethylhexyl)phthalate (DEHP)

CASRN — 117-81-7

Primary Synonym — Bis(2-ethylhexyl)phthalate

Last Revised — 09/07/1988

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 — B2; probable human carcinogen.

Basis — Orally administered DEHP produced significant dose-related increases in liver tumor responses in rats and mice of both sexes.

II.A.2. Human Carcinogenicity Data

Inadequate. Thiess et al. (1978) conducted a mortality study of 221 DEHP production workers exposed to unknown concentrations of DEHP for 3 months to 24 years. Workers were followed for a minimum of 5 to 10 years (mean follow-up time was 11.5 years). Eight deaths were reported in the exposed population. Deaths attributable to pancreatic carcinoma (1 case) and uremia (1 case in which the workers also had urethral and bladder papillomas) were significantly elevated in workers exposed for >15 years when compared to the corresponding age groups in the general population. The study is limited by a short follow-up period and unquantified worker exposure. Results are considered inadequate for evidence of a causal association.

II.A.3. Animal Carcinogenicity Data

Sufficient. In an NTP (1982) study, 50 male and 50 female Fisher 344 rats per group were fed diets containing 0, 6000 or 12,000 ppm DEHP for 103 weeks. Similarly, groups of 50 male and 50 female B6C3F1 mice were given 0, 3000 or 6000 ppm DEHP in the diet for 103 weeks. Animals were killed and examined histologically when moribund or after 105 weeks. No clinical signs of toxicity were observed in either rats or mice. A statistically significant increase in the incidence of hepatocellular carcinomas and combined incidence of carcinomas and adenoma were observed in female rats and both sexes of mice. The combined incidence of neoplastic nodules and hepatocellular carcinomas was statistically significantly increased in the high-dose male rats. A positive dose response trend was also noted.

Carpenter et al. (1953) found no malignant tumors in treated groups of 32 male and 32 female Sherman rats. Animals were given 400, 1300 or 4000 ppm DEHP in the diet for 1 year and reduced to a maximum of 8 males and 8 females and treated for another year. Controls, F1 and 4000 ppm groups were sacrificed after being maintained on control or 4000 ppm diets for 1 year.

Only 40 to 47% of the animals in each group, including F1 animals, survived 1 year. Thus, an insufficient number of animals were available for a lifetime evaluation.

Carpenter et al. (1953) did not find a carcinogenic effect in guinea pigs and dogs exposed to 1300 or 4000 ppm DEHP. Both guinea pigs and dogs were terminated after 1 year of exposure. The treatment and survival periods for these animals were considerably below their lifetimes.

II.A.4. Supporting Data for Carcinogenicity

Studies indicate that DEHP is not a direct acting mutagen in either a forward mutation assay in *Salmonella typhimurium* (Seed, 1982) or the rec assay in *Bacillus subtilis* (Tomita et al., 1982). DEHP did not induce mutations in a modified reverse mutation plate incorporation assay in *Salmonella* strains TA100 and TA98 at concentrations up to 1000 ug/plate in the presence or absence of S9 hepatic homogenate (Kozumbo et al., 1982). MEHP, the monoester form of DEHP and a metabolite is positive in the rec assay and in the reverse mutation assay in *Salmonella*. In the absence of exogenous metabolism MEHP produced chromosomal aberrations and sister chromatid exchanges in V79 cells. Both DEHP and MEHP induced chromosomal aberrations and morphological transformation in cultured fetal Syrian hamster cells exposed in utero (Tomita et al., 1982). Chromosomal effects were not found in CHO mammalian cells (Phillips et al., 1982) exposed to DEHP. DEHP was weakly positive with metabolic activation in only one of several studies testing for mutagenic activity at the thymidine kinase locus in L5178Y mouse lymphoma cells (Ashby et al., 1985). DEHP is a potent inducer of hepatic peroxisomal enzyme activity (Ganning et al., 1984).

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — $1.4E-2$ /mg/kg/day

Drinking Water Unit Risk — $4.0E-7$ per (ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
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Risk Level	Concentration
E-4 (1 in 10,000)	3E+2 ug/L
E-5 (1 in 100,000)	3E+1 ug/L
E-6 (1 in 1,000,000)	3E+0 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: hepatocellular carcinoma and adenoma
 Test animals: Mouse/B6C3Fl, male
 Route: diet
 Reference: NTP, 1982

-----Dose-----		
Administered (ppm)	Human Equivalent (mg/kg)/day	Tumor Incidence
0	0	14/50
3000	32	25/48
6000	65	29/50

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

In this study powdered rodent meal was provided in such a way that measured food consumption could include significant waste and spillage rather than true food intake. For this reason a standard food consumption rate of 13% mouse body weight was used in the dose conversion.

DEHP is hydrolyzed to monoesters including MEHP (Pollack et al., 1985; Lhuguenot et al., 1985; Kluwe, 1982). Although several species of animals have been determined to excrete

glucuronide conjugates of monoethylhexyl phthalate (MEHP) upon exposure to DEHP, rats do not (Tanaka et al., 1975; Williams and Blanchfield, 1975; Albro et al., 1982).

Slope factors based on combined hepatocellular carcinoma and neoplastic nodule incidences were $4.5E-3$ /mg/kg/day for female rats, $3.2E-3$ /mg/kg/day for male rats. A slope factor based on hepatocellular adenomas or carcinomas in female mice is $1.0E-2$ /mg/kg/day.

The unit risk should not be used if the water concentration exceeds $4E+4$ ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

An adequate number of animals was observed and a statistically significant increase in incidence of liver tumors was seen in both sexes and were dose dependent in both sexes of mice and female rats. A potential source of variability in the NTP study is the possibility of feed scattering. The above calculations are based on standard food consumption rates for mice (13% of body weight) and rats (5% of body weight).

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, 1988

The values in the 1988 Drinking Water Criteria Document for Phthalic Acid Esters (External Review Draft) have received Agency Review.

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

Agency Work Group Review — 08/26/1987, 10/07/1987

Verification Date — 10/07/1987

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 — Di(2-ethylhexyl)phthalate (DEHP)

CASRN — 117-81-7

Primary Synonym — Bis(2-ethylhexyl)phthalate

VI.A. Oral RfD References

Carpenter, C.P., C.S. Weil and H.F. Smyth. 1953. Chronic oral toxicity of di(2-ethylhexyl)phthalate for rats and guinea pigs. *Arch. Indust. Hyg. Occup. Med.* 8: 219-226.

NTP (National Toxicology Program). 1984. Di(2-ethylhexyl)phthalate: Reproduction and fertility assessment in CD-1 mice when administered by gavage. Final Report. NTP-84-079. NTP, Research Triangle Park, NC.

Shiota, K. and H. Nishimura. 1982. Teratogenicity of di-2-ethylhexyl phthalate and di-n-butyl phthalate in mice. *Environ. Health Perspect.* 45(0): 65-70.

Singhe, A.R., W.H. Lawrence and J. Autian. 1972. Teratogenicity of phthalate esters in rats. *J. Pharmacol. Sci.* 61: 51.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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Ashby, J., F.J. de Serres, M. Draper, et al. 1985. Evaluation of short-term tests for carcinogens. Report of the International Programme on Chemical Safety's Collaborative Study on In Vitro Assays. Elsevier Science Publishers, Amsterdam.

Carpenter, C.P., C.S. Weil and H.F. Smith, Jr. 1953. Chronic oral toxicity of di-(2-ethylhexyl)phthalate for rats, guinea pigs and dogs. *AMA Arch. Ind. Hyg. Occup. Med.* 8: 219-226.

Ganning, A.E., V. Brunk and G. Dallner. 1984. Phthalate esters and their effect on the liver. *Hepatology.* 4(3): 541-547.

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NTP (National Toxicology Program). 1982. Carcinogenesis bioassay of di-(2-ethylhexyl)phthalate (CAS No. 117-81-7) in F344 rats and B6C3F₁ mice (feed study). NTP Tech. Rep. Ser. TR No. 217, NTP, Research Triangle Park, NC.

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Pollack, G.M., R.C. Li, J.C. Ermer and D.D. Shen. 1985. Effects of route of administration and repetitive dosing on the disposition kinetics of di-(2-ethylhexyl)phthalate and its mono-de-esterified metabolite in rats. *Toxicol. Appl. Pharmacol.* 79: 246-256.

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

Tanaka, A., T. Adachi, T. Takahashi and T. Yamaha. 1975. Biochemical studies on phthalic esters. I. Elimination, distribution and metabolism of di-(2-ethylhexyl)phthalate in rats. *Toxicology*. 4: 253-264.

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Tomita, I., Y. Nakamura, N. Aoki and N. Inui. 1982. Mutagenic/carcinogenic potential of DEHP and MEHP. *Environ. Health Perspect.* 45: 119-125.

Williams, D.T. and B.J. Blanchfield. 1975. The retention, distribution, excretion and metabolism of dibutylphthalate-7-14C in the rat. *J. Agric. Food Chem.* 23: 854-857.

U.S. EPA. 1988. 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 — Di(2-ethylhexyl)phthalate (DEHP)

CASRN — 117-81-7

Primary Synonym — Bis(2-ethylhexyl)phthalate

Date	Section	Description
09/07/1988	II.	Carcinogen summary on-line

VIII. Synonyms

Substance Name — Di(2-ethylhexyl)phthalate (DEHP)

CASRN — 117-81-7

Primary Synonym — Bis(2-ethylhexyl)phthalate

Last Revised — 01/31/1987

- 117-81-7
- BEHP
- Bis(2-ethylhexyl)-1,2-benzene-dicarboxylate
- Bis(2-ethylhexyl)phthalate
- Bisoflex 81
- Bisoflex DOP
- Compound 889
- DAF 68
- DEHP
- Di(2-ethylhexyl)orthophthalate
- Di(2-ethylhexyl)phthalate
- Dioctyl phthalate
- Di-sec-octyl phthalate
- DOP
- Ergoplast FDO
- Ethylhexyl phthalate
- 2-Ethylhexyl phthalate
- Eviplast 80
- Eviplast 81
- Fleximel
- Flexol DOP
- Flexol plasticizer DOP
- Good-Rite GP 264
- Hatcol DOP
- Hercoflex 260
- Kodaflex DOP
- Mollan O
- NCI- C52733
- Nuoplaz DOP
- Octoil
- Octyl phthalate
- Palatinol AH
- Phthalic acid, Bis(2-ethylhexyl) ester
- Phthalic acid, dioctyl ester
- Pittsburgh PX-138
- Platinol DOP
- RC Plasticizer DOP
- RCRA waste number U028
- Reomol D 79P

- Reomol DOP
- Sicol 150
- Staflex DOP
- Truflex DOP
- Vestinol AH
- Vinicizer 80
- Witcizer 312