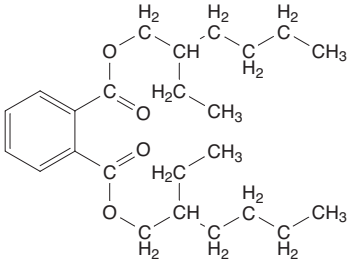
Di(2-ethylhexyl) Phthalate

CAS No. 117-81-7

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as DEHP, diethylhexyl phthalate, or dioctyl phthalate



Carcinogenicity

Di(2-ethylhexyl) phthalate (DEHP) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary exposure to DEHP caused benign and/or malignant liver tumors (hepatocellular adenoma and/or carcinoma) in mice and rats of both sexes, and the tumor incidences showed significant dose-related trends in both species (NTP 1982).

Since DEHP was listed in the *Third Annual Report on Carcinogens,* additional studies in rodents have been identified, which confirmed that DEHP caused liver tumors in rats and mice. DEHP also caused liver tumors in PPARα-null mice, which lack the peroxisome proliferator-activated receptor α (which has been proposed to be involved in DEHP-induced tumorigenesis) (Ito *et al.* 2007). In addition, dietary exposure to DEHP caused benign testicular tumors (Leydig-cell tumors) (Voss *et al.* 2005) and benign pancreatic tumors (acinar-cell and islet-cell adenoma) in male rats (Rao *et al.* 1990, David *et al.* 2000). Initiation-promotion studies in two strains of mice provided evidence that DEHP acted as a promoter of liver tumors (IARC 2000).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to DEHP (IARC 1982).

Properties

DEHP is a phthalate ester that exists as a colorless oily liquid with a slight odor. It is slightly soluble in water and carbon tetrachloride, miscible with mineral oil and hexane, and soluble in blood and body fluids containing lipoproteins. When heated to decomposition, it emits acrid smoke. DEHP is incompatible with nitrates, strong oxidizers, acids, and alkalis (HSDB 2010). DEHP is available in the United States in a variety of technical grades. Typical product specifications include 99.0% to 99.6% minimal ester content, 0.1% maximal moisture content, and 0.007% to 0.01% acidity (as acetic acid or phthalic acid) (IARC 2000). Physical and chemical properties of DEHP are listed in the table in the next column.

Property	Information
Molecular weight	390.6
Specific gravity	0.986 at 20°C/20°C
Melting point	–55°C
Boiling point	384°C
Log K_{ow}	7.6
Water solubility	0.27 mg/L at 25°C
Vapor pressure	1.42×10^{-7} mm Hg at 25°C

Source: HSDB 2010.

Use

About 95% of DEHP produced is used as a plasticizer in polyvinyl chloride (PVC) resins for fabricating flexible vinyl products (ATSDR 2002). Products typically contain from 1% to 40% DEHP; however, Tickner *et al.* (2001) reported that DEHP levels in PVC medical tubing may be as high as 80%. Plasticized PVC has been used in many consumer items and building products, such as tablecloths, shower curtains, furniture and automobile upholstery, imitation leather, garden hoses, floor tiles, swimming-pool liners, sheathing for wire and cable, rainwear, shoes, toys, dolls, baby pants, food packaging materials, tubing used in commercial milking equipment, and weather stripping (IARC 2000, ATSDR 2002, Bizzari *et al.* 2007). DEHP is also used in medical devices (blood and intravenous solution bags, catheters, tubing for dialysis and parenteral solutions, oxygen masks, and urine and colostomy bags) and in disposable surgical gloves. It has been used as a plasticizer in non-PVC materials, including polyvinyl butyral, natural and synthetic rubber, chlorinated rubber, ethyl cellulose, and nitrocellulose. In 2005, the breakdown of U.S. consumption of DEHP as a plasticizer was reported to be 40% for medical devices, 30% for consumer goods, and 30% for construction-related applications (Bizzari *et al.* 2007).

Non-plasticizer uses of DEHP include its use in dielectric fluids for electric capacitors, as an acaricide in orchards, as an inert ingredient in pesticides, in cosmetic products, as a vacuum-pump oil, to detect leaks in respirators, and in testing air-filtration systems. However, some of these applications are believed to be no longer in use or were never carried out on a commercial scale (IARC 2000, ATSDR 2002).

Historically, DEHP constituted about 50% of all the phthalate ester plasticizers used (IPCS 1992). However, the use of DEHP in some products has diminished because of health concerns and regulatory limitations on its use (ATSDR 2002, HCWH 2002). Furthermore, DEHP is being replaced by linear phthalates and other plastomers in many other applications, because of their superior performance and low toxicity (ATSDR 2002). In the United States, DEHP constituted roughly 10% of all plasticizers consumed in 2005; this was the smallest percentage of the total DEHP demand among the major world regions (compared with 18% in Western Europe, 52% in Japan, and 62.4% in "Other Asia").

Production

DEHP was first produced in the United States in 1939. Annual U.S. production remained fairly steady from 1975 to 2003, ranging from a peak of 180,000 metric tons (397 million pounds) in 1976 to a low of 109,000 metric tons (240 million pounds) in 1993. Total U.S. phthalate production in 2005 (the last year for which production data were available) was 88,000 metric tons (194 million pounds), accounting for 14.5% of total phthalate plasticizer production (Bizzari *et al.* 2007). In 2010, DEHP was available from 109 suppliers worldwide, including 45 U.S. suppliers (ChemSources 2010).

Exposure

The primary routes of potential human exposure to DEHP are ingestion, inhalation, and through medical procedures; exposure levels are highest for medical procedures (ATSDR 2002, NTP 2006). Dermal absorption is another potential exposure route; however, dermal absorption of DEHP *in vitro* is low (IARC 2000).

Evidence for exposure of the U.S. general population to DEHP comes from the 2013–2014 National Health and Nutrition Examination Survey, which detected four different monoester metabolites of the DEHP diester in urine. The metabolites generally showed a similar pattern of urinary levels. The highest levels were reported for mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), for which the geometric mean level in the general population was 9.57 μg/L (CDC 2018). The mean level in children aged 6 to 11 (18.2 μg/L) was almost twice the population mean, exceeding the levels in both adolescents (aged 12 to 19) and adults (20 or older). Higher levels of a contaminant in children are consistent with their greater exposure to many types of contaminants as a result of differences in ingestion of food and water and higher inhalation rates on a body-weight basis. Children also have a greater potential for exposure to contaminated soil outdoors and to contaminated dust and carpets indoors (EPA 2008).

Individuals receiving treatment with medical products containing DEHP are at risk for high DEHP exposure; exposure of newborn infants is of particular concern. For both adults and neonates, the highest estimated daily exposure levels were for blood transfusion, at 22.6 mg/kg of body weight for neonatal exchange transfusion and 8.5 mg/kg for transfusion in adult trauma patients. The U.S. Food and Drug Administration expressed special concern about aggregate exposure from repeated medical procedures, which often occurs in neonatal intensive-care settings. Other medical procedures that can result in DEHP exposure include hemodialysis, transfusion of platelets or plasma, pheresis, nasogastric feeding, and respirator use (FDA 2001). Long-term use of some procedures can result in significant total DEHP exposure. DEHP has been measured in large-volume parenteral formulations (i.e., fluids, nutrients, and electrolytes) and in whole blood and plasma stored in flexible-PVC bags (FDA 2001, ATSDR 2002). DEHP was found in condensate from respirator water traps at concentrations of up to 4,100 mg/L (IARC 2000).

Exposure to DEHP or its metabolites may occur in utero. DEHP and its major metabolite mono(2-ethylhexyl) phthalate (MEHP) were detected in cord blood collected from 84 newborns in Italy (Latini *et al.* 2003b), and MEHP was detected in 24% of 54 amniotic-fluid samples collected by amniocentesis (Silva *et al.* 2004).

A substantial fraction of the U.S. general population is exposed to measurable levels of DEHP because of its widespread use in consumer products and its presence in foods, beverages, and the environment. For the general population, the most important route of exposure is ingestion. DEHP has been found at low levels in packaged food as a result of its use as a plasticizer in products that contact food during its manufacture or storage (ATSDR 2002). DEHP has been detected in fish and other seafood, cheese, margarine, eggs, meat, cereal, baby food, milk, and infant formula. Because DEHP is lipophilic, higher levels are expected in fattier foods than in less fatty foods. In colostrum or milk from 17 healthy mothers, DEHP was detected in 16 of 17 samples and MEHP in 2 of 17 samples (Latini *et al.* 2003a). It has been estimated that more than 90% of daily intake of DEHP by noninfants is from dietary intake of food, water, and other beverages (Clark *et al.* 2003b). Daily exposure of adults in the general population was estimated to range from 1 to 30 μg/kg of body weight (0.001 to 0.03 mg/kg) (NTP 2006). Exposure may be several times as high in infants and toddlers, as a result of nondietary mouthing behaviors (e.g., chewing on soft-PVC plastic toys and ingesting household dust), with ingestion of household dust accounting for about half of total DEHP intake for infants (ATSDR 2002, Clark *et al.* 2003b). The concentration of DEHP in house dust was associated with the use of PVC-based flooring and wall coverings in the home; however, DEHP was also found in buildings that did not use PVC flooring or vinyl wall coverings (Bornehag *et al.* 2005). Based on limited data, concentrations of DEHP in house dust are expected to range from a few hundred to several thousand parts per million (IARC 2000, ATSDR 2002, Clark *et al.* 2003a, Rudel *et al.* 2003). Soft-PVC children's toys may contain DEHP, and children may ingest DEHP by sucking or chewing on the toys. DEHP was the most common plasticizer used in pacifiers and teethers until the early 1980s, when manufacturers voluntarily agreed to eliminate its intentional addition (ATSDR 2002). However, a study published in 2005 found that 12 of 18 such children's products contained DEHP at levels ranging from 20 to 840 ppm, including a teething ring that contained 410 ppm (Hileman 2005).

DEHP is considered a ubiquitous environmental contaminant and has been measured in outdoor and indoor air, water, sediment, and soil (IARC 2000, ATSDR 2002). DEHP is released to the environment from industrial facilities and waste-treatment plants. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of DEHP declined steadily from 4.9 million pounds in 1988 to 1.5 million pounds in 1997 and have since leveled off, with only minor variation from year to year. In 2008, releases of DEHP totaled around 960,000 lb (TRI 2010). In air, DEHP is expected to react with hydroxyl radicals, with an estimated half-life of about 6 hours. However, the expected adsorption of most DEHP to atmospheric particulates will decrease the reaction with hydroxyl radicals, resulting in a potentially longer atmospheric half-life. DEHP is readily removed from the atmosphere by rain or snow (ATSDR 2002).

DEHP in indoor air is due primarily to volatilization from consumer products and building materials that contain DEHP. In general, concentrations are expected to be higher in indoor air than in outdoor ambient air (ATSDR 2002). DEHP has also been measured at high air concentrations in cars. Some studies have suggested that because of DEHP's tendency to adsorb to airborne particulates, levels estimated based only on gas-phase measurements might underestimate total air levels. It was suggested that exposure to DEHP from indoor air may increase by a factor of up to three when particulate-matter contributions are accounted for (Øie *et al.* 1997).

DEHP has been detected in drinking water, surface water, groundwater, rainwater, and seawater, generally in the low parts-per-billion range. In water, DEHP is expected mainly to adsorb to suspended particulates; its evaporation from water is expected to be negligible (ATSDR 2002). However, its degradative half-life has been estimated to be roughly 10 hours in river water and 2 weeks in river sediment (Yuwatini *et al.* 2006). The main sources of DEHP released to land and soil are disposal of industrial and municipal waste to landfills and land application of DEHP-containing sludges (e.g., industrial or sewage sludges). Disposal of products containing flexible PVC, such as food wraps, may be a source of DEHP in municipal waste (IARC 2000). DEHP adsorbs strongly to soil, thus limiting losses from volatilization or leaching; however, co-disposal with common organic solvents could increase its solubility and its mobility in soil.

Air concentrations of DEHP in occupational settings (i.e., industrial production) may be significantly higher than general indoor levels. Occupational exposure to DEHP occurs primarily among workers involved in the manufacture and processing of DEHP and flexible-PVC plastics and plastic products, with inhalation of aerosols or mists the major route of exposure (IARC 2000, ATSDR 2002). DEHP is easily released into air at typical PVC-processing temperatures (Vainiotalo and Pfaffli 1990). However, few data are available on occupational exposure to DEHP. Air exposure levels of DEHP were reported to range from below the limit of detection to 4.1 mg/m^3 across various processes at a U.S. production facility. Higher urinary levels of DEHP, its metabolites, and total phthalates have been measured in DEHP-exposed workers than in non-exposed workers and in post-shift samples than in pre-shift samples (IARC 2000).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that pacifiers, rattles, and teethers shall not intentionally contain DEHP.
It is unlawful for any person to manufacture for sale, offer for sale, distribute in commerce, or import into the United States any children's toy or child-care article that contains DEHP at concentrations of more than 0.1%.

Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of DEHP is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Effluent Guidelines: Phthalate esters are listed as toxic pollutants.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.32 µg/L; based on fish or shellfish consumption only = 0.37 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of DEHP = U028.
Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.006 mg/L.

Food and Drug Administration (FDA, an HHS agency)

Limitations on the use of DEHP in basic components of single and repeated use food contact surfaces are prescribed in 21 CFR 177.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2018, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 5 mg/m^3.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 5 mg/m^3.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Immediately dangerous to life and health (IDLH) limit = 5,000 mg/m^3.
Recommended exposure limit (time-weighted-average workday) = 5 mg/m^3.
Short-term exposure limit (STEL) = 10 mg/m^3.
Listed as a potential occupational carcinogen.

References

ATSDR. 2002. *Toxicological Profile for Di(2-Ethylhexyl)Phthalate*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp9.pdf.

Bizzari SN, Blagoev M, Kishi A. 2007. Plasticizers. In *Chemical Economics Handbook.* Menlo Park, CA: SRI Consulting. Online edition. 148 pp.

Bornehag CG, Lundgren B, Weschler CJ, Sigsgaard T, Hagerhed-Engman L, Sundell J. 2005. Phthalates in indoor dust and their association with building characteristics. *Environ Health Perspect* 113(10): 1399-1404.

CDC. 2016. *Biomonitoring Summary: Phthalates Overview.* Centers for Disease Control and Prevention. Last updated: 12/23/16. https://www.cdc.gov/biomonitoring/DEHP_BiomonitoringSummary.html.

CDC. 2018. Urinary mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP). In *Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2018,* vol. 1. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. p. 486.

ChemSources. 2010. *Chem Sources - Chemical Search.* Chemical Sources International. http://www.chemsources.com/chemonline.html and search on diethylhexyl phthalate. Last accessed: 7/18/10.

Clark K, Cousins I, Mackay D, Yamada J. 2003a. Observed concentrations in the environment. In *The Handbook of Environmental Chemistry: Phthalate Esters,* vol. 3, part Q. Staples CA, ed. Berlin, Germany: Springer-Verlag. pp. 125-177.

Clark K, Cousins I, Mackay D. 2003b. Assessment of critical exposure pathways. In *The Handbook of Environmental Chemistry: Phthalate Esters,* vol. 3, part Q. Staples CA, ed. Berlin, Germany: Springer-Verlag. pp. 227-262.

David RM, Moore MR, Finney DC, Guest D. 2000. Chronic toxicity of di(2-ethylhexyl)phthalate in rats. *Toxicol Sci* 55(2): 433-443.

EPA. 2008. *Child-Specific Exposure Factors Handbook.* U.S. Environmental Protection Agency. https://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=484738.

FDA. 2001. *Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices*. U.S. Food and Drug Administration. http://www.fda.gov/cdrh/ost/dehp-pvc.pdf.

HCWH. 2002. *Aggregate Exposures to Phthalates in Humans*. Health Care Without Harm. http://www.noharm.org/lib/downloads/pvc/Agg_Exposures_to_Phthalates.pdf.

Hileman B. 2005. Panel ranks risks of common phthalate. *Chem Eng News* 83(46): 32-36.

HSDB. 2010. *Hazardous Substances Data Bank.* National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 7/18/10.

IARC. 1982. Di(2-ethylhexyl) phthalate. In *Some Industrial Chemicals and Dyestuffs.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 29. Lyon, France: International Agency for Research on Cancer. pp. 269-294.

IARC. 2000. Di(2-ethylhexyl) phthalate. In *Some Industrial Chemicals.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 77. Lyon, France: International Agency for Research on Cancer. pp. 41-148.

IPCS. 1992. *Environmental Health Criteria No. 131. Diethylhexyl Phthalate*. International Programme on Chemical Safety. http://www.inchem.org/documents/ehc/ehc/ehc131.htm.

Ito Y, Yamanoshita O, Asaeda N, Tagawa Y, Lee CH, Aoyama T, *et al.* 2007. Di(2-ethylhexyl)phthalate induces hepatic tumorigenesis through a peroxisome proliferator-activated receptor α-independent pathway. *J Occup Health* 49(3): 172-182.

Latini G, De Felice C, Del Vecchio A, Presta G, De Mitri B, Ruggieri R, Mazzeo P. 2003a. Lactational exposure to di-(2-ethylhexyl)-phthalate. *Ped Res* 54(4): 564.

Latini G, De Felice C, Presta G, Del Vecchio A, Paris I, Ruggieri F, Mazzeo P. 2003b. *In utero* exposure to di-(2-ethylhexyl)phthalate and duration of human pregnancy. *Environ Health Perspect* 111(14): 1783-1785.

NTP. 1982. *Carcinogenesis Bioassay of Di(2-ethylhexyl)phthalate (CAS No. 117-81-7) in F344 Rats and B6C3F$_1$ Mice (Feed Studies)*. Technical Report Series no. 217. Research Triangle Park, NC: National Toxicology Program. 127 pp.

NTP. 2006. *Draft NTP Brief on the Potential Human Reproductive and Developmental Effects of Di(2-ethylhexyl) Phthalate (DEHP)*. Research Triangle Park, NC: National Toxicology Program. 9 pp.

Øie L, Hersoug LG, Madsen JØ. 1997. Residential exposure to plasticizers and its possible role in the pathogenesis of asthma. *Environ Health Perspect* 105(9): 972-978.

Rao MS, Yeldandi AV, Subbarao V. 1990. Quantitative analysis of hepatocellular lesions induced by di(2-ethylhexyl)phthalate in F-344 rats. *J Toxicol Environ Health* 30(2): 85-89.

Rudel RA, Camann DE, Spengler JD, Korn LR, Brody JG. 2003. Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. *Environ Sci Technol* 37(20): 4543-4553.

Silva MJ, Reidy JA, Herbert AR, Preau JL Jr, Needham LL, Calafat AM. 2004. Detection of phthalate metabolites in human amniotic fluid. *Bull Environ Contam Toxicol* 72(6): 1226-1231.

Tickner JA, Schettler T, Guidotti T, McCally M, Rossi M. 2001. Health risks posed by use of di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review. *Am J Ind Med* 39(1): 100-111.

TRI. 2010. *TRI Explorer Chemical Report.* U.S. Environmental Protection Agency. http://www.epa.gov/triexplorer and select Di(2-Ethylhexyl) Phthalate. Last accessed: 7/18/10.

Vainiotalo S, Pfäffli P. 1990. Air impurities in the PVC plastics processing industry. *Ann Occup Hyg* 34(6): 585-590.

Voss C, Zerban H, Bannasch P, Berger MR. 2005. Lifelong exposure to di-(2-ethylhexyl)-phthalate induces tumors in liver and testes of Sprague-Dawley rats. *Toxicology* 206(3): 359-371.

Yuwatini E, Hata N, Taguchi S. 2006. Behavior of di(2-ethylhexyl) phthalate discharged from domestic waste water into aquatic environment. *J Environ Monit* 8(1): 191-196.