Chemical Information Profile

for

Diethyl Phthalate
[CAS No. 84-66-2]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

November 2006

Prepared by
Integrated Laboratory Systems, Inc.
Research Triangle Park, NC
Under Contract No. N01-ES-35515

Prepared for
National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
http://ntp.niehs.nih.gov/

Data Availability Checklist for Diethyl Phthalate [84-66-2]

Abbreviations: H = human; L = *Lepus* (rabbit); M = mouse; R = rat
Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

ENDPOINT	H	M	R	L
ADME				
Absorption	√	√	√	√
Distribution		√	√	√
Metabolism			√	
Excretion		√	√	√
Acute Toxicity (up to 1 week)				
Dermal				
Inhalation				
Injection		√	√	√
Ocular				√
Oral		√	√	√
Subchronic Toxicity (1 to <26 weeks)				
Dermal		√	√	
Inhalation				
Injection				
Oral		√	√	
Chronic Toxicity (≥26 weeks)				
Dermal			√	
Inhalation				
Injection				
Oral			√	
Synergism/Antagonism				
Synergistic effects				
Antagonistic effects				
Cytotoxicity				
Cytotoxic effects				
Reproductive Toxicity				
Fertility effects		√	√	√
Maternal effects		√	√	√
Paternal effects	√	√	√	√

ENDPOINT	H	M	R	L
Developmental Toxicity				
Developmental abnormalities		√	√	√
Embryonic/fetal effects		√	√	√
Newborn effects				
Carcinogenicity				
Dermal		√	√	
Inhalation				
Oral				
Anticarcinogenicity				
Anticarcinogenic effects				
Genotoxicity				
Cytogenetic effects		√		
Microbial gene mutation		√		
Gene mutation *in vitro*				
Gene mutation *in vivo*				
Germ cell effects				
Neurotoxicity				
Behavioral activity				
Motor activity				
Immunotoxicity				
Immunotoxic effects	√	√	√	
Mechanistic Data				
Target Organs/Tissues		√	√	
Endocrine modulation	√		√	
Effect on enzymes	√		√	
Modes of action				
Effect on metabolic pathways				
Structure-Activity Relationships		√	√	

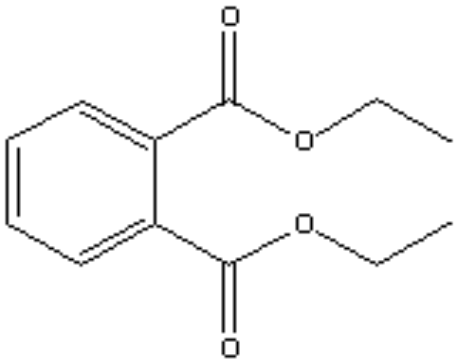
Diethyl Phthalate Nomination Summary

Chemical Name: Diethyl Phthalate

CAS RN: 84-66-2

Formula: $C_{12}H_{14}O_4$

Molecular Wt.: 222.24



Basis for Nomination: Diethyl phthalate (DEP) is nominated by the National Institute of Environmental Health Sciences for reproductive toxicity studies based on widespread exposure to the general population and inadequate data to evaluate its potential reproductive hazard. DEP is extensively used in consumer products, and recent biomonitoring data indicate that DEP and its metabolites are found at higher concentration in the urine of the general population than several other phthalates. Significant concern has been raised for phthalates regarding their endocrine disrupting properties and adverse effects on reproductive development in experimental animals. In a continuous breeding study in mice, there was a reduction in litter size at the highest dose level tested and a decrease in sperm concentration in offspring with no such effects in the parental generation. The mouse is known to be less sensitive to the reproductive effects of phthalates compared to rats, and a multigeneration reproductive study in rats has only recently been published. There were few developmental effects and no effects on reproductive performance observed in this well-conducted study. Limitations in the design of this study however, leave the question of potential reproductive hazard of DEP unanswered. Therefore, a second multigeneration reproductive toxicity study in rats that incorporates modern endocrine-related end points and sufficient numbers of animals retained in the F1 generation is needed to adequately define the dose response for reproductive toxicity and particularly the potential for effects in the F1 generation. Design parameters of a second multigeneration reproductive toxicity study should include assessment of the androgen status of F1 male offspring (e.g. measurement of anogenital distance and nipple retention perinatally and in adults) and retaining a minimum of two males and females per litter in the F1 generation.

A. Chemical Information

Molecular Identification

Chemical Name: Diethyl Phthalate (DEP)
CAS RN: 84-66-2
Synonyms: 1,2-Benzenedicarboxylic acid, diethyl ester; *o*-Benzenedicarboxylic acid diethyl ester; *o*-Bis(ethoxycarbonyl)benzene; Diethyl 1,2-benzenedicarboxylate; Diethyl *o*-phenylenediacetate; Diethyl *o*-phthalate; Di-*n*-ethyl phthalate; DPX-F5384; Ethyl phthalate; Phthalic acid, diethyl ester
Trade Names: Anozol, Estol 1550, Neantine, Palatinol A, Phthalol, Placidol E, Solvanol, Unimoll DA
Hill Formula: C12H14O4
Line Formula: C6H4(COOC2H5)2
Smiles Notation: CCOC(=O)C1=CC=CC=C1C(=O)OCC
PubChem CID: 6781
InChI: 1/C12H14O4/c1-3-15-11(13)9-7-5-6-8-10(9)12(14)16-4-2/h5-8H,3-4H2,1-2H3
Molecular Weight: 222.24
Purity of Commercial Products: 99.70 to 99.97% (IPCS, 2003)
Additives in Commercial Products: Not available
Impurities in Commercial Products: Isophthalic acid, terephthalic acid, maleic anhydride (IPCS, 2003)
Mammalian Metabolites: Ethanol, monoethyl phthalate (MEP), phthalic acid (Api, 2001 [PMID:11267702]; IPCS, 2003)
Biodegradation Products: carbon dioxide and methane (aerobic and anaerobic degradation by acclimated soil or activated sewage sludge); phthalic acid (primary degradation in soil) (IPCS, 2003)
Environmental Transformation:

- DEP reacts photochemically with hydroxyl radicals in the air (estimated half-life of 22.2 hours). Its distribution between the gaseous and particulate phases in air was estimated; the fraction of DEP in the particulate (aerosol) phase was 0.00039 (IPCS, 2003).
- DEP is mostly untransformed by photolysis (<1%); at DEP levels of 191 µg/L, only ~5% was lost by hydrolysis in 12 hours at pH 10 (IPCS, 2003).
- DEP does not adsorb to any aquatic surfaces (simulated aquatic ecosystem) (IPCS, 2003).

Physical-Chemical Properties

Physical State: colorless, oily liquid (IPCS, 2003; Labunska and Santillo, 2004)
Specific Gravity or Density Value: 1.12 g/mL @ 20 ºC (Api, 2001 [PMID:11267702])
Boiling Point: 295 ºC (ChemIDplus, 2004)
Vapor Pressure: 0.0021 mm Hg @ 25 ºC (ChemIDplus, 2004); 0.000345 mm Hg @ 20 °C (ATSDR, 1995)
Solubility: 1080 mg/L @ 25 ºC in water (ChemIDplus, 2004); soluble in alcohol, acetone, ether, benzene, ketones, esters, aromatic hydrocarbons, aliphatic solvents, and vegetable oils (IPCS, 2003)
Log P = Log K_{ow}: 2.42 (ChemIDplus, 2004), 2.47, 2.51 (IPCS, 2003), 1.4-3.3 (ATSDR, 1995)
Bioconcentration Factor (species): 117 (bluegill; *Lepomis macrochirus*) (IPCS, 2003)

B. Exposure Potential

U.S. Annual Production

1986, 1990, 1994, 1998, 2002: >10 – 50 million lb (U.S. EPA, 2005)

Worldwide Annual Production

Based on 1999 data, DEP production in European Union countries was reported around 10,000 metric tons and in Japan at 700 metric tons (IPCS, 2003).

Production Processes

DEP is produced by the reaction of phthalic anhydride with ethanol in the presence of concentrated sulfuric acid catalyst (IPCS, 2003).

Uses

DEP is used as a plasticizer in consumer products, including plastic packaging films, cosmetic formulations, and toiletries, and in medical treatment tubing (IPCS, 2003). It is used in various cosmetic and personal care products (e.g., hair sprays, nail polishes, and perfumes), primarily as a solvent and vehicle for fragrances and other cosmetic ingredients and as an alcohol denaturant (Labunska and Santillo, 2004). Other applications include as a camphor substitute, plasticizer in solid rocket propellants, wetting agent, dye application agent, diluent in polysulfide dental impression, and surface lubricant in food and pharmaceutical packaging (ATSDR, 1995).

Occupational Exposure

According to the NIOSH National Occupational Exposure Survey, conducted between 1981 and 1983, an estimated 239,149 U.S. workers (108,580 females) were potentially exposed to DEP in 16,408 facilities; employees in personal services (hairdressers, cosmetologists) and health services industries had the greatest exposure potential. In three rubber products manufacturing plants in Italy, DEP levels in workplace air were 0-120 µg/m^3 (shoe-sole factory), 0-30 µg/m^3 (vulcanization area of a tire-treading factory), 0-1 µg/m^3 (extrusion area of the retreading factory), and 1-3 µg/m^3 (extrusion area of an electrical cables insulation plant) (ATSDR, 1995).

Exposure Limits (Standards and Criteria)

ACGIH TLV: 5 mg/m^3 averaged over an 8-hour workshift (NJDHSS, 2002)

NIOSH REL: 5 mg/m^3 averaged over a 10-hour workshift (NJDHSS, 2002)

OSHA PEL: 5 mg/m^3 averaged over an 8-hour workshift (Api, 2001 [PMID:11267702]; ATSDR, 1995)

General Population Exposure

Greatest human exposure comes from the use of DEP-containing consumer products and the ingestion of contaminated foods (seafood, drinking water, or foods contaminated due to DEP leaching from packaging materials). Exposure may also occur via inhalation of contaminated air and from medical treatment involving use of polyvinyl chloride (PVC) tubing. Levels ranging from 18 to 26 mg/L DEP were found to leach from PVC dialysis tubing containing aqueous electrolyte solution perfused for 22-96 hours. Tubing perfused with human blood or bovine plasma for 8 hours showed DEP levels 2-4 times greater than water (IPCS, 2003).

Foods and Beverages, Cosmetics, etc.: DEP has been measured in packaged food at levels ranging from 2 to 5 ppm (ATSDR, 1995). DEP levels of 1.8, 1.2, and 5.3 µg/g were found in pies, crackers, and chocolate bars packaged in pie carton windows, paperboard box, and aluminum foil paper, respectively. In retort food (i.e., packaged ready-to-eat foods sealed usually in foil pouches), DEP ranged from 0 to 0.51 mg/kg. In Louisiana, oysters collected from the Inner Harbor Navigation Canal and clams from the Chef Menteur and Rigolets tributaries to Lake Pontchartrain contained 1110, 450, and 340 µg/kg DEP wet weight, respectively. Fish collected from Great Lakes tributaries in Wisconsin and Ohio in 1981 contained DEP in composite whole-body tissue samples ranging from <0.02 to <0.30 mg/kg. Fish taken from Siskiwit Lake on Isle Royale, Michigan, had higher DEP levels—0.4 mg/kg for lake trout and 1.7 mg/kg for whitefish (IPCS, 2003). DEP has been found in drinking water at levels ranging from 0.01 to 4.6 µg/L (ATSDR, 1995).

Food Tolerance Levels: Not available

Drinking Water Limits: Not available

Other Exposure Limits: Not available

Average Daily Intake: 13 µg/kg bw (U.S. women, 20-40 years); 90 µg/kg bw (95th percentile) (IPCS, 2003)

Dietary Intake Estimates: 4 mg, assuming daily ingestion of 1 kg of cellulose acetate-wrapped food containing 4 mg DEP/kg; 0.33 µg/kg bw/day from drinking water, assuming consumption of 2 L of water for a 60-kg person (IPCS, 2003)

Cosmetics: <0.1 to 28.6% (IPCS, 2003); analysis of 48 products detected DEP most frequently at concentrations up to 38,663 ppm (Hubenger & Havery, 2006)

Ambient Environment

Air Limit: Not available

Water Limit(s): 350 mg/L [ambient water quality criteria for protection of human health established by the U.S. EPA] (Api, 2001 [PMID:11267702])

Soil Limit: Not available

Levels in Tissues, Body Fluids, and Excreta: DEP was detected in 42% of human adipose tissue samples taken from children and adults (cadavers and surgical patients) in various U.S. regions; levels ranged from 0.20 µg/sample to 0.65 µg/g tissue wet weight (IPCS, 2003). Urine samples from the U.S. population, six years and older, from the National Health and Nutrition Examination Survey (1999-2002) had mean concentrations of MEP (metabolite of DEP and indicator of the amount of contact with DEP and other phthaltes) that ranged from 166.5 µg/L for the 50th percentile to 2670 µg/L for the 95th percentile; the geometric mean was 178.5 µg/L [144, 1905, and 178.5 µg/g of creatinine, respectively] (CDC, 2005). Median concentration of MEP reported in breast milk sampled from 130 Danish-Finnish women one to three months postnatally was 0.95 µg/L (range: 0.7 – 41.4 µg/L) (Main et al., 2006).

Environmental Occurrence

Natural Occurrence: Not known to occur naturally

U.S. Environmental Releases: Environmental releases are mainly the result of production and manufacturing of DEP; they also occur during the use and disposal of DEP-containing products. Releases to water or soil are expected be a result of leaching from landfills and into the atmosphere from combustion of plastics and from volatilization (IPCS, 2003).

- Air: estimated 72 metric tons annually due to manufacturing, use, or disposal (IPCS, 2003)
- Water: estimated 341 kg annually due to manufacturing, use, or disposal (IPCS, 2003)
- Land: estimated 364 kg annually due to landfill activities (IPCS, 2003)
- Other (specify): estimated 1.26 metric tons annually in total off-site releases (IPCS, 2003)

Toxics Release Inventory: Not subject to reporting (delisted in 1995)

Industries Represented: Not available

Number of Facilities: Not available

Hazardous Waste Sites: Yes _X_ No ___ No. of Facilities _248 of 1397 NPL sites_

0.0125 ppm in groundwater, 0.0121 ppm in surface water, and 0.039 ppm in soil (ATSDR, 1995)

Industrial Releases (non-TRI substance): DEP was found at a median concentration of <10 µg/L in 10% of industrial effluent samples and in 3.0% of ambient water samples in the USEPA's Storage and Retrieval (STORET) database. In 1982, the Nationwide Urban Runoff Program reported 0.5-11.0 µg/L DEP levels in 4% (three U.S. locations) of 86 samples (IPCS, 2003).

Mobile Sources: Not available

Municipal and Hospital Waste Incineration: Not available

Concentrations in Environmental Media

Surface Water:

- 0.00006-0.044 ppm in river water (ATSDR, 1995)
- 0.01-0.5 µg/L in North America and western European surface waters (USA, Canada, UK, Germany, Netherlands, and Sweden) from 1984-1997 (IPCS, 2003)
- 11.2 µg/L from the lower Tennessee River (IPCS, 2003)

Groundwater:

- 0.231 µg/L in sewage infiltrates of groundwater in Phoenix, Arizona; reduced to ≤0.017 µg/L in samples at 60-foot well depth (ATSDR, 1995)
- 0.26 µg/L from treatment of secondary effluents containing 1.9 µg/L DEP in Fort Polk, Louisiana (ATSDR, 1995)

Industrial Wastewater:

- 0.00001-0.060 ppm (ATSDR, 1995)
- 3.2 µg/L at textile industries (IPCS, 2003)
- 60 µg/L at a tire manufacturing plant (IPCS, 2003)

– 50 µg/L at a pulp and paper plant (IPCS, 2003)

Municipal Waste/Sewage: >10 µg/L in 6 wastewater samples from Canadian coal mine (DEP detected in 28 of 47 samples); 5 and 30 µg/g in sediments near the mine (ATSDR, 1995)

Ambient Air:

– 1.60-2.03 µg/m^3 in indoor air of telephone switching office in Newark, New Jersey (IPCS, 2003)
– 0.40-0.52 µg/m^3 in outdoor air in Newark, New Jersey (IPCS, 2003)
– 0-2.425 mg/g dust in settled dust from 346 bedrooms in Sweden (Bornehag et al., 2005)

Soils: 39 mg/kg [mean] in 4.26% samples from the National Priorities List hazardous waste sites (IPCS, 2003)

C. Toxicological Information

General Toxicity

Human Toxicity: Undiluted DEP did not cause primary skin irritation (Api, 1997; RIFM, 1968, 1973a, 1978d [all cited by Api, 2001; PMID:11267702]).

Animal Toxicity: DEP caused minimal eye irritation in rabbits. Undiluted DEP produced slight to moderate skin irritation in rabbits, rats, and guinea pigs (ATSDR, 1995; Draize et al., 1944; Klecak et al., 1977; RIFM, 1963, 1974, 1978c, 1984a, 1985, 1994 [all cited by Api, 2001; PMID:11267702]; Dear and Jassup, 1978 [cited by IPCS, 2003]; Lawrence et al., 1975 [cited by Api, 2001 [PMID:11267702], and IPCS, 2003]). In rats, chronic administration of pure DEP caused mild, dermal acanthosis (NTP, 1995; cited by IPCS, 2003).

Absorption, Disposition, Metabolism, and Elimination

Metabolism occurs by partial hydrolysis to ethanol and MEP. The principal urinary metabolite is MEP, and the minor secondary urinary metabolite is phthalic acid (Chambon et al., 1971; Kawano, 1980 [both cited by Api, 2001 [PMID:11267702]]). In humans, MEP has been detected in the urine, indicating absorption and metabolism of DEP (Blount et al., 2000b; cited by IPCS, 2003).

Dermal Administration

- In male F344 rats, after a single dermal application of DEP, 24% was excreted in urine and 1% in feces within 24 hours. After a week, 50% was excreted while 34% of the dose remained at the application site. Up to 0.5% of the dose was found in tissues (brain, lung, liver, spleen, small intestine, kidney, testis, spinal cord, and blood). Total recovery of radiolabel in urine, feces, tissues, and plastic cap (on application site) was 74% after 7 days (Elsisi et al., 1989 [cited by Api, 2001 [PMID:11267702], and IPCS, 2003]).
- In rabbits, dermal application caused ~27% excretion in the urine within 24 hours. After 4 days, 49% was excreted in urine and ~1% in feces. Blood levels contained ~7% of DEP after 1 hour and <1% of DEP after 4 days. The greatest amount of tissue distribution was found in the kidneys and liver (0.003 and 0.004%, respectively) (RIFM, 1973b; cited by Api, 2001 [PMID:11267702]).
- In rat dorsal skin *in vitro*, absorption was ~33% with occlusion and 38% without occlusion at 72 hours (Hotchkiss, 1988; Hotchkiss and Mint, 1994 [both cited by Api, 2001 [PMID:11267702]]; Mint et al., 1994 [cited by Api, 2001 [PMID:11267702], and IPCS, 2003]).
- In human breast skin *in vitro*, absorption was 3.5% with occlusion and 4.7% without occlusion at 72 hours (Hotchkiss, 1988; Hotchkiss and Mint, 1994; Mint et al., 1994 [all cited by Api, 2001 [PMID:11267702]]).
- In human epidermal abdominal skin and subcutaneous fat, lag time for DEP absorption was 6 hours and steady-state absorption rate was 12.8 µg/cm^2 per hour (Scott et al., 1987, 1989; cited by IPCS, 2003).

Oral Administration: When given orally, hydrolysis occurs in the lumen of the GI tract or the intestinal mucosal cells; when systemically absorbed, it occurs in organs such as the liver, kidney, and lung (Lake et al., 1976, 1977; Kayano et al., 1997; Rowland et al., 1977 [all cited by Api, 2001 [PMID:11267702]]).

- In mice and rats, oral administration of DEP (dose not provided) resulted in 47% excretion in the urine and 0.7% in the feces within 12 hours, 82 and 2.5% within 24 hours, and 90 and 2.7% within 48 hours. Maximum tissue distributions were in the kidney and liver, followed by blood, spleen, and fat; highest levels were seen at 20 minutes and trace amounts were seen at 24 hours (Ioku et al., 1976; cited by Api, 2001 [PMID:11267702]).
- In Wistar rats given DEP (10 or 100 mg) by stomach intubation, 77-78% of the administered dose was excreted in the urine within 24 hours as monoester derivative (67-70% of dose), phthalic acid (8-9%), or parent compound (0.1-0.4%). After one week, 85-93% was excreted (Kawano, 1980; cited by IPCS, 2003).

Intraperitoneal Administration: After i.p. administration of [^{14}C]carboxy-labeled DEP (2850 mg/kg bw) to pregnant rats on gestation day 5 or 10, maximum radioactivity was seen in maternal blood during the first 24 hours, which then quickly decreased. Amniotic fluid and fetal tissues showed a similar pattern. Radioactivity was transmitted across the placenta from mother to fetus for at least 15 days post-injection, distributed, and detected at <1% in maternal blood, placenta, amniotic fluid, and developing fetuses. Using a first-order excretion curve, a half-life of 2.22 days was calculated for DEP (Singh et al., 1975; cited by IPCS, 2003).

Acute Exposures

LC_{50}/LD_{50} Values:
oral LD_{50} = 6172 mg/kg [mouse] (ChemIDplus, 2004)
oral LD_{50} = 8600 mg/kg [mouse] (IPCS, 2003)
oral LD_{50} = 8600 mg/kg [rat] (ChemIDplus, 2004)
oral LD_{50} = 9200-9500 mg/kg [rat] (IPCS, 2003)
oral LD_{50} = 1000 mg/kg [rabbit] (ChemIDplus, 2004)
oral LD_{50} = 8600 mg/kg [guinea pig] (ChemIDplus, 2004)
i.p. LD_{50} = 2749 mg/kg [mouse] (ChemIDplus, 2004)
i.p. LD_{50} = 2800 mg/kg [mouse] (IPCS, 2003)
i.p. LD_{50} = 5058 mg/kg [rat] (ChemIDplus, 2004)
s.c. LD_{50} = 3000 mg/kg [guinea pig] (ChemIDplus, 2004)

Route:	intradermal injection
Species:	rabbits
Dose/Duration:	0.2 mL of 100 mg/mL emulsion; duration not provided
Observation Time:	10-26 minutes
Effects:	marked inflammatory reaction
Source(s):	Calley et al. (1966; cited by IPCS, 2003)

In rats, rabbits, chickens, and dogs, oral and intravenous administration of DEP caused stimulated respiration, lethargy, imbalance, cramps, and respiratory arrest (Blickensdorfer and Templeton, 1930; cited by IPCS, 2003).

Subchronic Exposures

Route:	oral (diet)
Species:	CD-1 mice, males and females
Dose/Duration:	0.25-5.0% (500-10,000 mg/kg/day) for 2 weeks
Observation Time:	not provided
Effects:	no deaths, toxic effects, or effects on body weight
Source(s):	NTP (1984; cited by Api, 2001 [PMID:11267702])

Route:	oral (diet)
Species:	Wistar rats, males and females
Dose/Duration:	10 – 50 mg/kg (0.57, 1.425, and 2.85 mg/kg/day) for 5 months
Observation Time:	not provided

Effects:	low dose: increase in liver-to-body weight ratio; liver vacuolations; fatty degeneration; number of hepatocyte peroxisomes; and serum acid phosphatase (ACP), lactate dehydrogenase (LDH), and alkaline phosphatase (ALT) levels. mid and high doses: mitochondrial proliferation and accumulation of glycogen, cholesterol, and triglycerides; loss of hepatic architecture at all doses; and decrease in total liver GSH at high as well as low dose.
Source(s):	(Pereira et al., 2006)
Route:	oral (diet)
Species:	Wistar rats, males
Dose/Duration:	2% (~2000 mg/kg bw/day) for 1 week
Observation Time:	not provided
Effects:	significant increase in relative liver weights; no effects on body weight, kidney weight, testes weight, or zinc levels in the liver, kidney, testes, or serum
Source(s):	Oishi and Hiraga (1980; cited by Api, 2001 [PMID:11267702], and IPCS, 2003)
Route:	oral (diet)
Species:	Fischer 344 rats
Dose/Duration:	2% (1753 mg/kg bw/day) for 3 weeks
Observation Time:	not provided
Effects:	slight but significant increased liver weight and activities of peroxisomal enzyme activities such as catalase and carnitine acetyltransferase; significant decrease in serum triglyceride level
Source(s):	Moody and Reddy (1978; cited by IPCS, 2003)
Route:	oral (drinking water)
Species	Sprague-Dawley rats
Dose/Duration:	50 mg/L with or without 5% ethyl alcohol for 120 days
Observation Time:	not provided
Effects:	no significant increase in body weight, liver weight, or water consumption; significant increase in serum aspartate and alanine aminotransferase levels, liver glycogen levels, and liver cholesterol levels; enhanced lipid peroxidation in livers
Source(s):	Sonde et al. (2000; cited by IPCS, 2003)
Route:	oral (diet)
Species	Sprague-Dawley rats, males and females
Dose/Duration:	0.2, 1, or 5% (150-3710 mg/kg/day) for 16 weeks
Observation Time:	not provided
Effects:	decreased food intake and body weight gain in mid- and high-dose females and in high-dose males; increased weights of the brain, liver (significant in females at all doses), kidneys, stomach, small intestine, and full cecum at the high dose. NOAEL = 750 mg/kg bw/day
Notes:	Increased organ weights relative to body weight were considered due to reduced body weight gain; increased liver weight was due to hypertrophy.
Source(s):	Brown et al. (1978; cited by Api, 2001 [PMID:11267702], and IPCS, 2003)
Route:	oral (*per os*)
Species	guinea pigs
Dose/Duration:	125, 250, 500, or 1000 mg/kg, 5 or 6 days/week for up to 12 weeks
Observation Time:	not provided

Effects:	histopathologic damage in the liver and kidney at the high dose; questionable changes at the mid doses
Source(s):	RIFM (1983b; cited by Api, 2001 [PMID:11267702])

Route:	dermal
Species:	B6C3F$_1$ mice, males and females
Dose/Duration:	12.5, 25, 50, or 100 µL (560-5000 mg/kg bw/day), 5 days/week for 4 weeks
Observation Time:	not provided
Effects:	increased absolute and relative liver weights in females at 25 and 100 µL
Source(s):	NTP (1995; cited by Api, 2001 [PMID:11267702], and IPCS, 2003)

Route:	dermal
Species:	Sprague-Dawley rats, male and female
Dose/Duration:	2 mL/kg/day (6-hour semiocclusive patch) for 2 weeks
Observation Time:	not provided
Effects:	no changes in body weight gain, clinical chemistry, hematology, or histology
Source(s):	RIFM (1994; cited by Api, 2001 [PMID:11267702])

Route:	dermal
Species:	F344/N rats, males and females
Dose/Duration:	37.5, 75, 150, or 300 µL (200-2500 mg/kg bw/day), 5 days/week for 4 weeks
Observation Time:	not provided
Effects:	increased relative liver weights in 150 µL females and 300 µL males and females; increased relative kidney weights in 150 µL males and females and 300 µL males
Source(s):	NTP (1995; cited by Api, 2001 [PMID:11267702], and IPCS, 2003)

Chronic Exposures

Route:	dermal
Species:	B6C3F$_1$ mice, males and females
Dose/Duration:	7.5, 15, or 30 µL (~260, 520, or 1050 mg/kg/day), 5x/week for up to 103 weeks
Observation Time:	not provided
Effects:	no significant toxicity (survival and mean body weights similar to controls); no effects on hematological or blood clinical chemistry parameters; no dermatotoxicological lesions (including neoplasms and non-neoplastic lesions); increased incidence of basophilic foci in liver of mid-dose males
Source(s):	Marsman et al. (1994; cited by Api, 2001 [PMID:11267702]) NTP (1995; cited by Api, 2001 [PMID:11267702], and IPCS, 2003)

Route:	oral (diet)
Species:	rats (species not provided), males and females
Dose/Duration:	0.5, 2.5, or 5% (~250, 1250, or 2500 mg/kg/day) for 2 years
Observation Time:	not provided
Effects:	slight decrease in body weight gain at all doses and reduced food consumption at the high dose; no treatment-related effects on hemocytology, blood sugar, nonprotein nitrogen levels, urinalyses, or post-mortem pathology
Source(s):	RIFM (1955; cited by Api, 2001 [PMID:11267702])

Route:	dermal
Species:	F344/N rats, males and females

Dose/Duration:	100 or 300 µL (320 or 1010 mg/kg bw in males; 510 or 1560 mg/kg bw in females) 5 days/week for 2 years
Observation Time:	not provided
Effects:	slight decrease in body weight gain; dose-related increase of minimal to mild epidermal acanthosis at the application site in both sexes (considered an adaptive response to local irritation); decrease in incidence of fatty degeneration of liver; no effects on hematological or blood clinical chemistry parameters
Source(s):	NTP (1995; cited by Api, 2001 [PMID:11267702], and IPCS, 2003)

Synergistic/Antagonistic Effects

Synergistic effect on toxicity reported in 21-day-old male and female pups from mating of Wistar rats fed polychlorinated biphenyls (PCBs) + DEP, or PCBs or DEP alone, based on serum and liver ACP, LDH, and ALT levels and liver histology (Pereira and Rao, 2006)

Cytotoxicity

Not available

Reproductive and Developmental Toxicity

Human Studies

- Mean motility in sperm suspensions from volunteers was time- and dose-dependently decreased when exposed *in vitro* with DEP (33, 330, 3300 µmol/L); ~10% inhibition was seen at the high dose (Fredricsson et al., 1993; cited by Api, 2001 [PMID:11267702], and IPCS, 2003).
- Two studies examined effect of phthalates on male reproductive development based on MEP content in breast milk or urine samples tested during late pregnancy. Correlation between lower androgen activity and Leydig cell function in healthy boys and MEP content in mother's breast milk was reported (Main et al., 2006). An inverse correlation between maternal urinary MEP and anogenital distance in male offspring 2 – 36 months of age was reported and suggests prenatal exposure to phthalates may effect male reproductive development (Swan et al., 2005). [Note: The validity and biological plausibility of this study have been questioned (McEwen and Renner, 2006).]

Animal Studies

Mice

- In CD-1 mice given DEP (4500 mg/kg bw/day) via gavage on gestation days 6-13, no effects on maternal body weight gain, number of viable litters, neonatal survival, or neonatal weight gain were reported (Hardin et al., 1987 [cited by Api, 2001 [PMID:11267702], and IPCS, 2003]).
- In pregnant Jcl:ICR mice, percutaneous administration of DEP (500, 1600, or 5600 mg/kg/day) on gestation days 0-17, maternal toxicity was observed—reduced thymus and spleen weights at all doses and increased adrenal weight at high dose. Decreased fetal body weight and an increased incidence of cervical and lumbar ribs were seen at the high dose. NOAEL = 1600 mg/kg bw/day for dam and offspring (Tanaka et al., 1987 [cited by Api, 2001[PMID:11267702], and IPCS, 2003]).
- In a continuous breeding study, Swiss CD-1 mice given DEP (0.25, 1.25, or 2.5% [340, 1770, or 3640 mg/kg bw/day]) in the diet showed no adverse effects on the physiology, fertility, or reproductive performance in F_0 generation. At the high dose, F_1 generation showed decreases in body weight gain, number of live pups per litter (sexes combined), sperm levels, and uterus and pituitary weight (females). Increases in prostate weight were observed in males and in liver weight in females. LOAEL estimated to be 3640 mg/kg bw/day (Chapin and Sloane, 1997 [cited by IPCS, 2003]; Lamb et al., 1987; NTP, 1984 [both cited by Api, 2001 [PMID:11267702], and IPCS, 2003]; Morrissey et al., 1989 [cited by Api, 2001 [PMID:11267702]]).

Rats

- Male and female Wistar rats fed DEP (2.85 mg/kg bw/day) in the diet for 100 days (plus 10 days during mating and 40 days during gestation to weaning) had no effect on reproductive ability. Male and female offspring (21 days old) had increased serum and liver ACP and LDH as well as

increased serum ALP levels; liver ALP was significantly decreased in male pups and unchanged in females; liver-to-body weight ratios were increased in males and decreased in females; and mild liver vacuolations were reported for both male and female pups (Pereira and Rao, 2006).

- Two generational study: Male and female SD rats (F_0) were given DEP in diet (600, 3000, or 15000 ppm) for 10 weeks prior to mating and throughout mating, gestation, and weaning period (males ~15 weeks; females ~17 weeks); F_1 parents (21 – 25 days old) received same treatment. No significant adverse effects were seen in clinical observations, gross histopathology, or reproductive parameters of F_0 and F_1 parents [Note: Slight decrease in serum testosterone level in F_0 males, inhibition of body weight gain before weaning in F_1 and F_2 females, and delay in vaginal opening in F_1 females were seen, but changes were not significant] (Fujii et al., 2005).
- Male rats administered DEP (1600 mg/kg bw/day) via oral intubation once or for up to 4 days showed no effect on testicular and accessory gland weight and histopathology. Additionally, there was no effect on progesterone binding to testes microsomes, testicular cytochrome P-450 content, or testicular steroidogenic enzyme activity (Foster et al., 1980, 1983; Gray and Butterworth, 1980; Oishi and Hiraga, 1980 [all cited by Api, 2001 [PMID:11267702], and IPCS, 2003]).
- Male Wistar rats given DEP (2% [~2000 mg/kg bw]) in their diet for one week had decreased testosterone levels in testes and serum but showed no testicular damage (Foster et al., 1980; Gray and Butterworth, 1980; Oishi and Hiraga, 1980 [all cited by Api, 2001 [PMID:11267702], and IPCS, 2003]).
- Male Wistar rats given DEP (2000 mg/kg) daily for 2 days via gavage exhibited mitochondrial swelling, smooth endoplasmic reticulum focal dilation and vesiculation, and increased intestinal macrophage activity associated with surface Leydig cells; there was no effect on seminiferous tubular structure or Leydig cell morphology (Jones et al., 1993 [cited by Api, 2001 [PMID:11267702], and IPCS, 2003]).
- In CD rats given DEP (0.25, 2.5, or 5% [200, 1900, or 3300 mg/kg bw/day]) in feed on gestation days 6-15, maternal toxicity was observed—decreases in food and water consumption and in body weight gain. There were no effects on embryo/fetal growth, viability, or malformations (external, visceral, or skeletal) except for an increased incidence of one extra rib in offspring from the high-dose group. NOAEL = 2.5% for mother and offspring (Field et al., 1993; Price et al., 1989 [both cited by Api, 2001 [PMID:11267702], and IPCS, 2003]; NTP, 1988 [cited by Api, 2001 [PMID:11267702]]).
- In pregnant Sprague-Dawley rats given DEP (750 mg/kg bw/day) via gavage from gestation day 14 to postnatal day 3, male offspring showed no effects on the weights of the genital organs (testis, seminal vesicle, prostate, epididymis, or penis), liver, pituitary, or adrenal gland; on the incidence of malformation; or on body weights. NOAEL = 750 mg/kg bw/day (Gray et al., 2000; cited by IPCS, 2003).

Rabbits

- Repeated dermal application of 50% DEP (2 mL/kg) on gestation days 6-18 resulted in no maternal or fetal toxicity, and no effects on fetal development was observed (CIR, 2003).

Carcinogenicity

Human Studies: Not available

Animal Studies: Two-year dermal studies showed no evidence of carcinogenicity in rats and equivocal evidence of carcinogenicity in mice.

- In $B6C3F_1$ mice, DEP (7.5, 15, or 30 µL [260-1100 mg/kg/day]) caused increased incidences of combined hepatocellular adenoma/carcinoma in high-dose males. In low- and mid-dose females, the incidence was higher than in the high-dose or control groups (Marsman et al., 1994 [cited by Api, 2001 [PMID:11267702]]; NTP, 1995 [cited by Api, 2001 [PMID:11267702], and IPCS, 2003]).
- In F344/N rats, DEP (100 or 300 µL [320 or 1015 mg/kg in males; 520 or 1600 mg/kg/day in females]) resulted in a decrease in incidence of mammary gland fibroadenomas in female rats

(Marsman et al., 1994 [cited by Api, 2001 [PMID:11267702]]; NTP, 1995 [cited by Api, 2001 [PMID:11267702], and IPCS, 2003]).

- No tumor initiating or promoting activity of DEP (0.1 mL) was observed when applied to Swiss CD-1 mice as an initiator (followed by TPA administration) or as a promoter (after DMBA administration) for one year (Marsman et al., 1994 [cited by Api, 2001 [PMID:11267702]]; NTP, 1995 [cited by Api, 2001 [PMID:11267702], and IPCS, 2003]).

Anticarcinogenicity

Human Studies: Not available

Animal Studies: Not available

Genetic Toxicity

Microbial Gene Mutation: Equivocal results were reported (Api, 2001 [PMID:11267702]; IPCS, 2003).

- mutagenic in *Salmonella typhimurium* strains TA100 and TA1535 without S9 (Agarwal et al., 1985; Kozumbo et al., 1982 [both cited by IPCS, 2003])
- nonmutagenic in strains TA98 and TA1537 with or without S9 (Agarwal et al., 1985; Rubin et al., 1979 [both cited by IPCS, 2003])
- nonmutagenic in strains TA98, TA100, TA1535, or TA1537 with or without S9 (NTP, 1995 [cited by Api, 2001 [PMID:11267702], and IPCS, 2003]; Zeiger et al., 1982, 1985 [cited by IPCS, 2003])

Human Studies (*in vitro* and *in vivo*): Not available

Animal Studies (*in vitro* and *in vivo*)

Gene Mutation: Not available

Cytogenetic Effects: No chromosome aberrations in Chinese hamster ovary cells, with or without S9; induction of sister chromatid exchanges (SCE) at 167-750 µg/mL with S9; similar findings in Chinese hamster fibroblasts with SCE at 0.05-0.5 µg/L (NTP, 1995 [cited by Api, 2001 [PMID:11267702], and IPCS, 2003]; Ishidate and Odashima, 1977 [cited by IPCS, 2003]).

Germ Cell Effects: Not available

Neurotoxicity

Human Studies: Not available

Animal Studies: Dietary DEP (up to 3710 mg/kg) for 2 or 16 weeks resulted in increased relative brain weights but no effect on the gross or microscopic pathology of the brain or sciatic nerve of rats (Brown et al., 1978; cited by IPCS, 2003). Dermal exposure of DEP (up to 855 mg/kg bw) for 2 years had no effect on brain weights in rats or mice (NTP, 1995; cited by IPCS, 2003).

Immunotoxicity

Human Studies: DEP caused no dermal sensitization reactions in normal volunteers as well as patients, including perfume-sensitive patients, contact dermatitis patients, children with dry plantar dermatosis, one with skin sensitivity to tea tree oil, and one with psoriasis. Positive patch tests reactions, however, have been reported in patients with contact dermatitis from eyeglasses frames and hearing aids, as well as from the plastic of a computer mouse known to contain phthalates. Positive patch test results were also reported in 1/30 workers with and 1/30 workers without dermatitis in a shoe factory using polyvinyl chloride granulate (e.g., de Groot and Weyland, 1992; Greif, 1967; Ishihara, 1977; Larsen, 1977; Meynadier et al., 1986; Oliwiecki et al., 1991; and RIFM, 1978d [all cited by Api, 2001 [PMID:11267702], and/or IPCS, 2003]).

Animal Studies: Undiluted DEP was not a dermal sensitizer in guinea pigs (Klecak, 1979; Klecak et al., 1977; RIFM, 1978e [all cited by Api, 2001 [PMID:11267702]]). Dietary DEP had no effect on the gross or microscopic pathology of lymph nodes or the thymus in rats, while dermal exposure of DEP had no effect on the histopathology of the spleen, thymus, lymph nodes, or thyroid/brain weights of mice or rats (Brown et al., 1978; NTP, 1995 [both cited by IPCS, 2003]).

D. Mechanistic Data

Target Organs/Tissues

Human: Not available

Animal: Liver

Endocrine Modulation

Human: DEP was not estrogenic in *in vitro* recombinant/receptor gene bioassay with HeLa cells and human breast cancer cell line ZR-75 but exhibited weak activity in human breast cancer cell line MCF-7 and in yeast cells with human estrogen receptor (hER) (Api, 2001 [PMID:11267702]). DEP also did not induce cell proliferation in MCF-7 cells (Hong et al. 2005).

Animal: DEP was not estrogenic in immature female Wistar rats, recombinant yeast strain (*Saccharomyces cerevisiae*) containing hER and lac-Z, or in *in vitro* estrogen receptor-binding assay using rat uterine cytosol (Api, 2001 [PMID:11267702]).

Effect on Enzymes

Human: Not available

Animal: DEP inhibited uridine diphosphate glucuronyl transferase and *p*-nitrophenol-glucoronyl transferase activity of rat liver microsomal preparations *in vitro* but had no effect on *N*-acetyltransferase and microsomal cytochrome P-450 (ATSDR, 1995).

Modes of Action

Human: Not available

Animal: In rats, DEP produced mitochondrial swelling and smooth endoplasmic reticulum focal dilation or vesiculation in Leydig cells (IPCS, 2003).

Effect on Metabolic Pathways

Activation: Not available

Perturbation: Not available

Structure-Activity Relationships

Isomers: Not available

Congeners: Contrary to DEP, other phthalate esters caused effects on testicular Sertoli cell function and on testicular cell cultures (Api, 2001 [PMID:11267702]). In developmental studies in rats, di(2-ethylhexyl) phthalate and benzyl butyl phthalate produced shortened anogenital distances and decreased testis weights or other genital organ weights in male offspring (IPCS, 2003). Other effects of some phthalates include malformations of the epididymis and vas deferens, undescended testes, and hypospadias. Dibutyl phthalate and monobutyl phthalate have also caused reproductive and developmental effects in mice and rats.

Reactive Moieties: Not available

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Acknowledgements

Support to the National Toxicology Program for the preparation of Chemical Information Profile for Diethyl Phthalate was provided by Integrated Laboratory Systems, Inc., through NIEHS Contract No. N01-ES-35515. Contributors included: Scott A. Masten, Ph.D. (Project Officer, NIEHS); Marcus A. Jackson, B.A. (Principal Investigator, ILS, Inc.); Bonnie L. Carson, M.S. (ILS, Inc.); Claudine A. Gregorio, M.A. (ILS, Inc.); Yvonne H. Straley, B.S. (ILS, Inc.); and Nathanael P. Kibler, B.A. (ILS, Inc.).

Search Strategy

Brief Internet searches with the Google search engine resulted in the following URLs of good review documents regarding diethyl phthalate:

ATSDR (1995)
http://www.atsdr.cdc.gov/toxprofiles/tp73.pdf

IRIS (2002)
http://www.epa.gov/iris/subst/0226.htm

Labunska and Santillo (2004) [Greenpeace] (5 pp.)
http://www.greenpeace.to/publications_pdf/DEP_2004.pdf

IPCS CICAD (2003)
http://www.inchem.org/documents/cicads/cicads/cicad52.htm

PAN Pesticide Database
http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PC34029

In addition, the U.S. EPA Inventory Update Rule database was checked for any production information for the assigned chemical (http://www.epa.gov/opptintr/iur/iur02/search03.htm).