Phthalates
TEACH Chemical Summary

U.S. EPA, Toxicity and Exposure Assessment for Children’s Health
This TEACH Chemical Summary is a compilation of information derived primarily from U.S. EPA and ATSDR resources, and the TEACH Database. The TEACH Database contains summaries of research studies pertaining to developmental exposure and/or health effects for each chemical or chemical group. TEACH does not perform any evaluation of the validity or quality of these research studies. Research studies that are specific for adults are not included in the TEACH Database, and typically are not described in the TEACH Chemical Summary.

I. INTRODUCTION

Phthalates are a group of chemicals used as plasticizers, which provide flexibility and durability to plastics such as polyvinyl chloride (PVC). Phthalates are dialkyl or alkyl aryl esters of 1,2-benzenedicarboxylic acid. Phthalates in pure form are usually clear liquids, some with faint sweet odors and some with faint yellow color (1-6). Plastics that contain phthalates are commonly used in applications that include building materials, clothing, cosmetics, perfumes, food packaging, toys, and vinyl products (e.g., flooring, shower curtains, and rain coats); and in medical applications that include blood transfusion bags and tubing, intravenous fluid bags and tubing, and other medical devices. Phthalates are also found in lubricating oils, solvents, and detergents (1-6).

With respect to health effects, phthalates are often classified as endocrine disruptors or hormonally-active agents (HAAs) because of their ability to interfere with the endocrine system in the body (6, 7). Exposure to phthalates has been reported to result in increased incidence of developmental abnormalities such as cleft palate and skeletal malformations, and increased fetal death in experimental animal studies (1-7). The most sensitive system is the immature male reproductive tract, with phthalate exposure resulting in increased incidence of undescended testes, decreased testes weight, decreased anogenital distance (distance between the anus and the base of the penis), and other effects (1-7).

The ubiquitousness of phthalates in items used daily by children is of concern for children’s health because it increases the likelihood of exposure. Exposure media of concern for children include breast milk, retail cow’s milk, and infant formulas (8-10); foods contained in plastic packaging (6, 11-13); plastic toys and feeding items, such as cups and bowls (12-15); indoor air (16); and medical devices such as plastic tubing used during intravenous treatments, transfusions, extracorporeal membrane oxygenation (ECMO) treatments, or dialysis (17-26). The use of phthalates in bottle nipples and pacifiers was voluntarily discontinued beginning in 1986 (1-6, 27).

Unless stated otherwise, most studies described in this Chemical Summary focused on diethylhexyl phthalate (DEHP) exposure, one of the most commonly used and produced phthalates in the United States. Other phthalates of concern include: diisononyl phthalate (DINP), butyl benzyl phthalate (BBP), diethyl phthalate (DEP), di-n-butyl phthalate (DnBP), di-n-octyl phthalate (DnOP), dimethyl phthalate (DMP), and dimethyl-terephthalate (DMT).
### II. EXPOSURE MEDIA AND POTENTIAL FOR CHILDREN’S EXPOSURE

<table>
<thead>
<tr>
<th>Exposure Media</th>
<th>Relative Potential for Children’s Exposure</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Higher</td>
<td>Phthalates can be found throughout the diet, including infant formulas and baby food. Phthalates can leach into foods heated in plastic containers. Mouthing of toys containing phthalates can also result in phthalate exposure. Individuals receiving multiple treatments, feedings, or transfusions through medical tubing containing phthalates are likely to be exposed to phthalates. Infants in Neonatal Intensive Care Units (NICU) are one group of concern for phthalate exposure.</td>
</tr>
<tr>
<td>Dermal</td>
<td>Medium</td>
<td>Some cosmetics, fragrances, and lotions may contain phthalates. Some insect repellants also contain phthalates.</td>
</tr>
<tr>
<td>Indoor Air</td>
<td>Lower</td>
<td>Indoor air concentrations can be increased from offgassing of building materials such as new vinyl flooring or newly painted rooms. Phthalates have been measured in house dust.</td>
</tr>
<tr>
<td>Ambient Air</td>
<td>Lower</td>
<td>Ambient air is generally not considered a significant exposure media.</td>
</tr>
<tr>
<td>Sediment</td>
<td>Lower</td>
<td>Sediment is generally not considered an environmental medium of concern.</td>
</tr>
<tr>
<td>Soil</td>
<td>Lower</td>
<td>Phthalates are not generally found in soil.</td>
</tr>
<tr>
<td>Drinking Water</td>
<td>Lower</td>
<td>Phthalates have been detected in drinking water, though generally at low concentrations.</td>
</tr>
</tbody>
</table>

1. For more information about child-specific exposure factors, please refer to the Child-Specific Exposure Factors Handbook ([http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145](http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145)).
2. The Relative Potential for Children’s Exposure category reflects a judgment by the TEACH Workgroup, U.S. EPA, that incorporates potential exposure pathways, frequency of exposure, level of exposure, and current state of knowledge. Site-specific conditions may vary and influence the relative potential for exposure. For more information on how these determinations were made, go to [http://www.epa.gov/teach/teachprotocols_chemsumm.html](http://www.epa.gov/teach/teachprotocols_chemsumm.html).
3. Childhood represents a lifestage rather than a subpopulation, the distinction being that a subpopulation refers to a portion of the population, whereas a lifestage is inclusive of the entire population.
4. Information described in this column was derived from several resources (e. g. , 1-5) including studies listed in the TEACH Database ([http://www.epa.gov/teach](http://www.epa.gov/teach)).
III. TOXICITY SUMMARY\textsuperscript{5, 6}

Phthalates are a group of numerous chemicals, which share a common chemical structure (see Introduction). Some phthalates are classified as “endocrine disruptors” for their ability to modify the endocrine, or hormonal, system. Only certain phthalates have toxicity reference values listed through U.S. federal agencies. The phthalates listed in this section are those for which toxicity reference values are available. Toxicity information for individual phthalates is listed separately for each phthalate. An identified “critical data need” is for information on the effects of mixture of phthalates including questions of additivity and interference (28).

\textbf{Butyl benzyl phthalate (BBP)}

One study reported that increased incidences of eczema and rhinitis in children were associated with increased concentrations of BBP in house dust (29). Prenatal exposure of rats to BBP resulted in teratogenic effects in offspring that included skeletal malformations, increased incidence of cleft palate, and decreased number of live fetuses at birth (30-32). Defects in male rat reproductive organ development following prenatal exposure included increased incidence of undescended testicles, hypospadias (urethra on the underside of the penis), and other anatomical differences (33-35). A two-generation study reported similar effects in offspring, and in addition, delayed puberty in both sexes (36). Pregnant rats exposed to BBP had reductions in ovarian and uterine weights, progesterone levels, and ovulatory follicles (37, 38). In adult female rats, BBP exposure resulted in increased incidence of mononuclear cell leukemia and liver effects, including increased liver size (6).

\textbf{Metabolites}: A metabolite of BBP, mono-n-butyl phthalate (MBP), has been shown to be teratogenic in rats following maternal exposure during pregnancy, leading to increased fetal death and increased fetal skeletal malformations (31, 39-45). Increased incidence of undescended testes, decreased testes weight, and decreased anogenital distance were also observed following MBP exposure during development (46-48).


Note: BBP is currently undergoing reassessment in IRIS (49).

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\textsuperscript{5} Please refer to research article summaries listed in the TEACH Database for details about study design considerations (e.g., dose, sample size, exposure measurements).

\textsuperscript{6} This toxicity summary is likely to include information from workplace or other studies of mature (adult) humans or experimental animals if child-specific information is lacking for the chemical of interest. Summaries of articles focusing solely on adults are not listed in the TEACH Database because the TEACH Database contains summaries of articles pertaining to developing organisms.

\textsuperscript{7} For recent information pertaining to carcinogen risk assessment during development, consult “Guidelines for Carcinogen Risk Assessment and Supplemental Guidance on Risks from Early Life Exposure” at http://www.epa.gov/cancerguidelines.
**Dibutyl phthalate (DBP)**

Prenatal exposure of rats to DBP resulted in teratogenic effects in offspring that included skeletal malformations, increased incidence of cleft palate, and decreased number of live fetuses at birth (30, 50-52). Defects in male reproductive organ development following prenatal exposure to DBP included increased incidence of undescended testicles, hypospadias, and other anatomical differences (34, 53-66). Decreased testosterone (60), decreased pituitary hormones (67), and delayed puberty (56) were associated with prenatal DBP exposure. Exposure to DBP during adulthood resulted in increased mortality in rats (4).

**Metabolites:** Mono-N-butyl phthalate (MBP) is a metabolite of DBP (see Toxicity Summary for metabolites of BBP on the previous page).

**Carcinogenicity weight-of-evidence classification:** The U.S. EPA classified DBP as class D, “Not Classifiable,” stating that “pertinent data regarding carcinogenicity was not located in the available literature” (http://www.epa.gov/iris/subst/0038.htm), and the WHO IARC has not evaluated DBP (http://monographs.iarc.fr/ENG/Classification/index.php).

Note: DBP is currently undergoing reassessment in IRIS (49).

**Di(2-ethylhexyl)phthalate (DEHP)**

Increased incidence of asthma in children was associated with increased DEHP concentrations in house dust (29). Exposure of some infants and children to DEHP from medical devices was associated with cholestasis (reduced bile flow) (19) and unusual lung disorders (21). Another study of adolescents who were exposed to DEHP during ECMO treatments as infants reported no adverse effects on several hormone levels tested (68).

Prenatal exposure of rats to DEHP resulted in teratogenic effects in offspring that included skeletal malformations, increased incidence of cleft palate, and decreased number of live fetuses at birth (69, 70). Defects in male reproductive organ development following prenatal exposure of rats to DEHP included increased incidence of undescended testicles, hypospadias, and other anatomical differences (34, 35, 71-73). Decreased sperm production (71) and decreased testosterone levels (72) were also reported. Prenatal exposure of rats to DEHP led to adverse effects on lung tissue development (74). Exposure of neonatal, suckling, and adult rats to DEHP resulted in reduced hepatic enzyme activities (75-77). DEHP exposure resulted in anovulation (lack of release of eggs from the ovaries) in adult female rats (1, 6).

**Metabolites:** Metabolites of DEHP, MEHP and 2-ethylhexanoic acid, have been shown to be teratogenic in rats and mice, with effects including skeletal abnormalities and exencephaly (brain growth outside of the skull) in offspring (78-81).

*Continued on next page*
Di(2-ethylhexyl)phthalate (DEHP) continued

**Carcinogenicity weight-of-evidence classification:** The U.S. EPA classified DEHP as class B2, probable human carcinogen (under the 1986 U.S. EPA guidelines), based on increased liver tumors in adult male and female rats ([www.epa.gov/iris/subst/0014.htm](http://www.epa.gov/iris/subst/0014.htm), II.A.1). The WHO IARC classified DEHP in 2000 as “Not Classifiable” (Group 3) as to carcinogenicity, based on inadequate evidence in humans, and sufficient evidence in experimental animals ([http://monographs.iarc.fr/ENG/Monographs/vol77/volume77.pdf](http://monographs.iarc.fr/ENG/Monographs/vol77/volume77.pdf)).

Note: DEHP is currently undergoing reassessment in IRIS (49).

**Diethyl phthalate (DEP)**

Prenatal exposure of rats to DEP resulted in skeletal variations and delayed ossification (hardening) of bones in offspring (82). Prenatal and lactational exposure to DEP resulted in abnormal sperm and decreased testosterone in male offspring during adulthood (83). In adult rats, DEP exposure resulted in increased liver weights (3). The U.S. EPA recently reassessed available DEP toxicity information and concluded that DEP is minimally or mildly toxic via the oral or dermal route; upon review the U.S. EPA noted that increased incidence of extra ribs in offspring was observed at maternally toxic doses, and concluded that “there was no evidence of increased susceptibility in a rat reproductive study” (84).

**Carcinogenicity weight-of-evidence classification:** The U.S. EPA has classified diethyl phthalate as class D, not classifiable as to carcinogenicity (under the 1986 U.S. EPA Cancer Guidelines), because pertinent data regarding carcinogenicity was not located in the available literature (85). The U.S. EPA OPPTS recently concluded that DEP is neither mutagenic nor carcinogenic (84). The WHO IARC has not evaluated DEP ([http://monographs.iarc.fr/ENG/Classification/index.php](http://monographs.iarc.fr/ENG/Classification/index.php)).

**Dimethyl terephthalate (DMT)**

Exposure of adult rats to DMT was associated with chronic kidney inflammation (6).

**Carcinogenicity weight-of-evidence classification:** U.S. EPA IRIS has not completed evaluation pertaining to carcinogenicity of DMT ([http://www.epa.gov/iris/subst/0046.htm](http://www.epa.gov/iris/subst/0046.htm)). The WHO IARC has not evaluated DMT ([http://monographs.iarc.fr/ENG/Classification/index.php](http://monographs.iarc.fr/ENG/Classification/index.php)).

Supporting references and summaries are provided in the TEACH Database at [http://epa.gov/teach/](http://epa.gov/teach/).

Last revised 10/10/2007: includes research articles through 2005, and other information through 2006.
IV. EXPOSURE AND TOXICITY STUDIES FROM THE TEACH DATABASE

This section provides a brief description of human and animal studies listed in the TEACH Database. These descriptions generally include the overall conclusion in each study without evaluation or assessment of scientific merit by TEACH. For more details about doses and exposure levels, query the TEACH Database. Any consideration of adverse events should include an understanding of the relative exposure on a body weight basis. In many cases, exposure levels in animal studies are greater than exposure levels normally encountered by humans.

A. HUMAN EXPOSURE AND EFFECTS

- One recent study of adult males in Sweden found significantly fewer motile sperm for men with higher urine concentrations of the phthalate metabolite MEP (86). Reduced sperm motility (motion) was significantly associated with blood concentrations of some polychlorinated biphenyls (PCBs) and urine concentrations of some phthalate metabolites (e.g., MBeP and PCB 153) (87).

- Infants and children can be exposed to phthalates through several dietary sources (8, 9, 11, 88, 89). Phthalates were found in every sample analyzed of baby food and infant formula in a Danish study (8). DEHP and other phthalates were found in almost all of the analyzed milk, cream, butter, and cheese samples tested in a study that included the United Kingdom, Norway, and Spain (9). Furthermore, phthalates were found in food samples packaged in plastics, and the presence of phthalates was attributed to plastic residues from the packaging (11) or from plastic gloves used in packaging the food (88).

- Infants and children can be exposed to phthalates through mouthing of plastic toys, and use of plastic eating containers. Phthalates, mainly DEHP and diisononyl phthalate (DINP), are found in some plastic products that children use, such as toys and plastic food containers (1, 6, 15); phthalates can be extracted from these products into a solution that mimics saliva (12, 14). The quantity of phthalate exposure to children from toys remains equivocal, and difficult to quantitate. One study in Holland estimated the amount of DEHP and DINP ingested by children under 3 years of age from toys by measuring leaching of these phthalates into solution (14). Another study in the U.S. by the Consumer Product Safety Commission concluded that levels of DINP leached from a different panel of toys did not pose a significant risk to children (13).

- Phthalate concentrations in particulate dust collected in homes suggested that inhalation of phthalates may be an important route of exposure for some children (27, 29, 90-92). Both BBP (29, 91) and DEHP (27, 29) have been detected in house dust. One study in Sweden detected phthalates in dust in 38 out of 372 homes tested (29). However, a study looking at house dust found no significant association between metabolites in children’s urine and DEHP levels in house dust (90).

- As evidence of exposure, phthalates and their metabolites have been measured in blood and urine of pregnant women (93), infants and children (24, 29, 90, 94-102), and also in breast milk (95). Metabolites of DEHP include mono-ethylhexyl phthalate (MEHP) and 2-ethylhexanoic acid (2-EHA); metabolites of DnBP include mono-n-butyl phthalate (MBP); and metabolites of BBP include MBP and mono-n-benzyl phthalate (MBeP).
Chemical Summary, Phthalates (continued)

- Newborn infants may be exposed to phthalates from some medical procedures. Neonates are exposed to DEHP when receiving medical intervention with PVC-containing devices (i.e., intravenous [I.V.] tubing which may contain 20-40% DEHP by weight) (1). DEHP and its toxic metabolite monoethylhexyl phthalate (MEHP) have been measured in the serum of neonates following blood transfusions and intravenous fluid administration (17, 18, 95, 97), extracorporeal membrane oxygenation (ECMO) (19, 20, 68), mechanical ventilation (21), and intravenous parenteral feeding with nutrients (22, 23).

- Infants and children exposed to phthalates from specific medical interventions have been reported to have some health effects that correlated with the exposure. In infants who underwent ECMO, a significant association was found between the degree of cholestasis (reduced bile formation or flow) and increasing DEHP serum levels (19). Another study reported an unusual lung disorder in three pre-term infants who were artificially ventilated with tubing containing DEHP (22). In contrast, another study found no acute effects in pre-term infants who had increased serum levels of DEHP (25). Also, adolescents who had been exposed to DEHP during ECMO as infants were reported to have normal levels of testosterone and pituitary hormones during adolescence (68).

- Recent evidence in humans provides evidence that maternal exposure to phthalates during pregnancy can adversely affect male reproductive tract development. Specifically, decreased anogenital distance (the distance between the anus and the base of the penis) in boys ages 2-36 months was significantly associated with increased maternal urine concentrations of four phthalate metabolites (MEP, MBP, monobenzyl phthalate, and monoisobutyl phthalate (MiBP) (103).

- A Swedish study on persistent allergic symptoms in children found significant positive associations between incidence of rhinitis or incidence of eczema and BBP concentrations; and between incidence of asthma and DEHP concentrations in household dust (29).

- Premature thelarche (breast development) was significantly associated with plasma concentrations of DEHP, DBP, DEP, DMP, and the DEHP metabolite MEHP in a case control study of young girls in Puerto Rico (94).

B. EXPERIMENTAL ANIMAL EXPOSURE AND EFFECTS
There are numerous experimental animal studies that have examined health effects of phthalates during development. The studies summarized here represent some of the more recent studies available in the literature through 2005. Comprehensive and detailed summaries of animal studies are available for individual phthalates elsewhere (see Considerations for Decision Makers in this Chemical Summary) (1-6).

- The tissue distribution and metabolism of phthalates have been studied in experimental animals. Young mice injected with DEHP retained a minimal amount in the brain (104). In rats, phthalates and their metabolites have been shown to cross the placenta, and to pass into offspring through breast milk when pregnant or lactating rats were exposed by injection (75, 105, 106) or ingestion (76, 107-109).

- Maternal exposure to phthalates during pregnancy has been shown to be teratogenic (cause birth defects) in offspring. The specific phthalates shown to have effects on fetuses following maternal

Supporting references and summaries are provided in the TEACH Database at http://epa.gov/teach/
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chemical summary, phthalates (continued)

Ingestion include DnBP (50-52); DEHP and its metabolites, MEHP and 2-EHA (41, 69, 70, 78); BBP and its metabolites, MBP and MBeP (30-32, 39); as well as DEP and DMP (82). Two studies of prenatal exposure to phthalates demonstrated no effects on fetuses, with one study using inhalation exposure of pregnant rats to DEHP (110), and another study using injection of pregnant rabbits with the DEHP metabolite, MEHP (111). The U.S. EPA reported toxicology studies demonstrating minimal or no developmental toxicity in offspring exposed in utero (84).

- Observed teratogenic effects (birth defects) following prenatal phthalate or phthalate metabolite exposure included skeletal variations in ribs and sterna, and delayed ossification (hardening) of bones (30-32, 42, 50, 78, 82, 112-114); increased pre- and post-implantation loss (fetal death) and decreased number of live fetuses (37-40, 52, 63, 70, 114); increased incidence of malformations of the forebrain, optic system, and mandibular and maxillary processes (50); decreased fetal body weight (70); increased incidence of cleft palate (30-32, 39, 51, 52); and increased dilation of the renal pelvis (30-32, 39).

- Teratogenic effects following prenatal exposure to phthalates were dependent on the stage of pregnancy when exposed (31, 42, 112), on the water solubility of the phthalate (113), and on the stereochemical form of the phthalate (78). Teratogenic effects on fetuses (skeletal malformations and testicular dysgenesis) were noted when pregnant dams were exposed by ingestion (31, 42, 112) or by injection (78, 113).

- In support of the classification of phthalates as endocrine disruptors, sexual development of males has been affected by exposure to phthalates and their metabolites. Ingestion exposure of pregnant rats to DEHP (35, 71-73, 115), BBP (33, 35), or DBP (53-67, 115) resulted in male offspring with an increased incidence of hypospadias; decreased testicular and plasma testosterone levels; abnormal Sertoli and Leydig cells in testicles; shortened anogenital distances; and female-like nipples. Similar effects were seen in male rabbits exposed to DBP in utero and during adolescence, but not exposed as adults (116). The DBP-induced effects in rats were similar to those seen in human testicular dysgenesis syndrome (TDS) (55). Some other studies of neonatal ingestion exposure found no significant effects on male reproductive system development for DEHP (117), DBP (62), or BBP (118).

- Metabolites of phthalates are thought to be the biologically active compounds that exert developmental effects following phthalate exposure. Exposure to the metabolites MBP (31, 39-42) or MEHP (78, 108, 111) resulted in skeletal malformations and testicular development abnormalities, as seen with exposure to the phthalates BBP or DEHP.

- Major adverse changes in neonatal lung tissue were noted following prenatal exposure to DEHP via maternal ingestion, such that changes in lung tissue resulted in an estimated 50% decrease in the ability of lung cells to exchange gas (74).

Supporting references and summaries are provided in the TEACH Database at [http://epa.gov/teach/](http://epa.gov/teach/). Last revised 10/10/2007: includes research articles through 2005, and other information through 2006.
Exposure to DEHP (76, 77) or DBP (119) via ingestion has been shown to affect several hepatic enzyme activities in fetal, neonatal, suckling, and adult rats. Suckling rats exposed to DEHP through maternal milk had significant increases in hepatic peroxisomal enzyme activities (palmitoyl CoA oxidase and carnitine acetyltransferase) (76); these effects were also observed in neonatal and adult male rats following oral exposure to DEHP (77). Furthermore, suckling rats exposed to DEHP through maternal milk had significant decreases in several other hepatic enzyme activities (aniline hydroxylase, ethylmorphine N-demethylase, and arylhydrocarbon hydroxylase) and in cytochrome P450 content (75).

Behavioral effects in young rats exposed to DEHP via intracisternal injection (inside the brain) have been reported (120, 121). Exposed mice experienced significant, dose-dependent increases in motor activity, and this model is being explored as a model for attention-deficit hyperactivity disorder (ADHD) in children (120, 121).

V. CONSIDERATIONS FOR DECISION-MAKERS

This section contains information that may be useful to risk assessors, parents, caregivers, physicians, and other decision-makers who are interested in reducing the exposure and adverse health effects in children for this particular chemical. Information in this section focuses on ways to reduce exposure, assess possible exposure, and, for some chemicals, administer treatment.

Information about Reducing or Preventing Exposure

- The daily levels of exposure to DEHP for the general public may approach or exceed the U.S. EPA RfD, 0.02 mg/kg/day (equivalent to 1.4 mg/day for an average 70-kg person); see Toxicity Reference Values section of this Chemical Summary. Compiling estimates from several studies, the average total daily individual exposure to DEHP in the U.S. was estimated to be 0.003-0.03 mg/kg/day in one report (1), and 0.006-0.02 mg/kg/day in another report (16).

- The likelihood of exposure of children to phthalates is quite high, given that phthalates are plasticizers that can leach out of polyvinyl chloride and other plastic products widely used in the U.S. (2-6, 8-12, 14, 15, 88). Children ages 3-12 months are at highest risk for exposure to phthalates from leaching from plastic toys by mouthing (1, 6).

- Quantifying exposures of children from mouthing of toys has been difficult for numerous reasons, but exposures are likely to be low (1, 5, 6, 122, 123). Many manufacturers have voluntarily stopped the use of phthalates in nipples, teethers, and rattles; and many retailers voluntarily refuse to sell such products if they contain phthalates (1, 122).
Premature infants and other children who require dialysis, prolonged feeding, or mechanical ventilation via plastic tubing are at risk for significant exposure to phthalates in medical devices (1, 6, 9, 11, 15). Neonatal exposure to DEHP and MEHP, via exchange transfusion, can be up to 3,300 µg/kg and 360 µg/kg, respectively, per transfusion (17, 18). Recently the U.S. EPA National Toxicology Program (NTP) issued a report that included a concern for critically-ill male infants who may be exposed to DEHP in medical tubing (124). The U.S. FDA also recommended reducing use of DEHP-containing tubing in some medical procedures, including exchange transfusions and ECMO treatments of infants (125).

The U.S. Food and Drug Administration (FDA) urges careful use of plastic containers to reheat food in the microwave (126, 127). Recommendations include: 1) microwave-safe plastic wrap should be placed loosely over food so that steam can escape, and should not directly touch your food; 2) carryout containers from restaurants and margarine tubs should not be used in the microwave; and 3) containers that hold prepared microwavable meals after you use them because they are meant for one-time use.

Other Exposure Information

Concentrations of phthalate metabolites in urine of children six years of age and older were measured for the National Health and Nutrition Examination Survey (NHANES) (128). This ongoing comprehensive national survey is administered by the U.S. Centers for Disease Control and Prevention National Center for Health Statistics (129). A total of 12 phthalate metabolites were measured as part of this study.

Some jurisdictions have set regulations that limit or ban phthalate use in children’s toys.

--The use of six phthalates in children’s toys and childcare articles have been banned in Europe by the European Parliament: use of BBP, DBP, DEHP in toys and childcare articles; use of DINP, DIDP, and DNDP in toys and childcare articles that are put in children’s mouths (130).

--The San Francisco government has banned the manufacture, sale, and distribution within the metropolitan area of toy or child care article or child feeding product intended for use by a child that is made with or contains more than 0.1% of these phthalates: DEHP; DBP; BBP; DINP; DnOP; and diisononyl phthalate (131, 132).

Detailed toxicological summaries of the phthalates BBP, DEHP, DINP, DBP, DnOP, diisodecyl phthalate, and di-n-hexylphthalate are provided in a series of monographs (issued in 2003) and expert panel reports (issued in 2000) provided by the U.S. National Toxicology Program; a recent 2006 draft report is available for DEHP (6). Detailed Toxicological Profiles are also available from the U.S. ATSDR for DEHP (1), DEP (3), DBP (4), and DnOP (5). Hazard Summaries are available from the U.S. EPA for DBP (133), DMP (134), and DEHP (135). A recent evaluation of DEP by the U.S. EPA OPPTS is available (84).
Some phthalates are listed by the U.S. EPA as inert (or “other”) ingredients in pesticides, indicating the ingredient is not an “active” ingredient for the product, but may require evaluation or has been evaluated as to its potential toxicity to humans. Many inert ingredients are categorized by the U.S. EPA according to level of concern for toxicity to humans. There are 10 phthalates included on the EPA inert pesticide ingredient list, with the phthalate of highest concern being phthalic acid, bis(2-ethylhexyl) ester C1980 on List 1, Inert Ingredients of Toxicological Concern (136). DEP was recently reevaluated as an inert, and the U.S. EPA concluded that DEP is minimally toxic via the oral and dermal routes (84).

Other Information Resources

Three phthalates (BBP, DBP, and DEHP) are listed on the 2005 Priority List of Hazardous Substances for the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) section 104 (i), as amended by the Superfund Amendments and Reauthorization Act (SARA). This is a list, in the order of priority of concern, of substances most commonly found at sites listed on the National Priorities List (NPL); there are currently 275 substances on this list. The phthalate DBP is listed as number 52, DEHP is listed as number 76, and BBP is listed as number 195 on the NPL (137). DEHP has been identified in at least 737 of 1,613 hazardous waste sites proposed for inclusion on the NPL (1).

Consult the U.S. EPA “Child-Specific Exposure Factors Handbook” (EPA-600-P-00-002B) for factors to assess children’s ingestion and inhalation rates (138). An updated External Draft of the 2006 version of this handbook is available (139).

VI. TOXICITY REFERENCE VALUES

Phthalates consist of numerous chemicals, only some of which have toxicity reference values listed through U.S. federal agencies. The phthalates listed in this section are those for which toxicity reference values are available.

Butyl benzyl phthalate (BBP)

A. Oral/Ingestion

U.S. EPA Reference Dose (RfD) for Chronic Oral Exposure: $2 \times 10^{-1}$ (or 0.2) mg/kg/day, based on significantly increased liver-to-body weight and liver-to-brain weight ratios in adults (www.epa.gov/iris/subst/0293.htm, I.A.1) (140). Last Workgroup Verification Date 6/15/89.

B. Inhalation

Not available.

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Chemical Summary, Phthalates (continued)

*Dibutyl phthalate (DBP)*

**A. Oral/Ingestion**

U.S. EPA Reference Dose (RfD) for Chronic Oral Exposure: 1E-1 (or 0.1) mg/kg/day, based on increased mortality in adult animals ([www.epa.gov/iris/subst/0038.htm](http://www.epa.gov/iris/subst/0038.htm), I.A.1) (141). Last Workgroup Verification Date 1/22/86.

U.S ATSDR Minimal Risk Level (MRL): Oral acute exposure, 0.5 mg/kg/day, based on developmental effects ([www.atsdr.cdc.gov/mrls.html](http://www.atsdr.cdc.gov/mrls.html)) (142). Last revised 9/01.

**B. Inhalation**

U.S ATSDR Minimal Risk Level (MRL): Oral acute exposure, 0.5 mg/kg/day, based on developmental effects ([www.atsdr.cdc.gov/mrls.html](http://www.atsdr.cdc.gov/mrls.html)) (142). Last revised 9/01.

*Di(2-ethylhexyl)phthalate (DEHP)*

**A. Oral/Ingestion**

U.S. EPA Reference Dose (RfD) for Chronic Oral Exposure: 2E-2 (or 0.02) mg/kg/day, based on increased relative liver weight in adult animals ([www.epa.gov/iris/subst/0014.htm](http://www.epa.gov/iris/subst/0014.htm), I.A.1) (143). Last Workgroup Verification Date 1/22/86.

U.S. EPA Cancer Oral Slope Factor: 1.4E-2 (or 0.014) per mg/kg/day, based on hepatocellular carcinoma and adenoma, using the linearized multistage procedure, extra risk ([www.epa.gov/iris/subst/0014.htm](http://www.epa.gov/iris/subst/0014.htm), II.B.1) (143). Last Workgroup Verification Date 10/7/87.

U.S. EPA Cancer Drinking Water Unit Risk: 4.0E-7 (or 0.0000004) per (μg/L) ([www.epa.gov/iris/subst/0014.htm](http://www.epa.gov/iris/subst/0014.htm), II.B.1) (143). Last Workgroup Verification Date 10/7/87.

U.S. EPA Drinking Water Concentrations at Specified Risk Levels for Cancer: E-4 (or 1 in 10,000), 3E+2 (or 300) μg/L; E-5 (or 1 in 100,000), 3E+1 (or 30) μg/L; E-6 (or 1 in 1,000,000), 3E+0 (or 3.0) μg/L ([www.epa.gov/iris/subst/0014.htm](http://www.epa.gov/iris/subst/0014.htm), II.B.1) (143). Last Workgroup Verification Date 10/7/87.

U.S. EPA Maximum Contaminant Level (MCL) for Drinking Water: 0.006 mg/L, based on reproductive difficulties, liver problems, and increased risk of cancer in adult animals ([www.epa.gov/safewater/mcl.html#mcls](http://www.epa.gov/safewater/mcl.html#mcls)) (144). Last revised 7/02.

U.S. EPA Maximum Contaminant Level Goal (MCLG): 0 mg/L. Last revised 7/02.

U.S. ATSDR Minimal Risk Level (MRL): Oral intermediate exposure, 0.1 mg/kg/day, based on reproductive effects in adult animals. Oral chronic exposure, 0.06 mg/kg/day, based on reproductive effects in adult animals ([www.atsdr.cdc.gov/mrls.html](http://www.atsdr.cdc.gov/mrls.html)) (142). Last revised 9/02.

Continued on next page
B. Inhalation
Not available.

_Diethyl phthalate (DEP)_

A. Oral/Ingestion

_U.S. EPA Reference Dose (RfD) for Chronic Oral Exposure:_ 8E-1 (or 0.8) mg/kg/day, based on decreased growth rate, food consumption and altered organ weights in adult rats [http://www.epa.gov/iris/subst/0226.htm, I.A.1] (85). Last Workgroup Verification Date 7/16/87.

B. Inhalation
Not available.

_Dimethyl phthalate (DMP)_

A. Oral/Ingestion


B. Inhalation

_U.S. EPA Reference Concentration (RfC) for Chronic Inhalation Exposure:_ available health effects data were insufficient to derive an RfC [http://www.epa.gov/iris/subst/0353.htm, I.B.] (145). Last Workgroup Verification Date 7/26/90.

_Dimethyl terephthalate (DMT)_

A. Oral/Ingestion

_U.S. EPA Reference Dose (RfD) for Chronic Oral Exposure:_ 1E-1 (or 0.1) mg/kg/day, based on chronic kidney inflammation in adult rats [http://www.epa.gov/iris/subst/0046.htm, I.A.1] (146). Last Workgroup Verification Date 10/9/85.

_U.S. ATSDR Minimal Risk Level (MRL):_ Oral acute exposure, 7 mg/kg/day, based on reproductive effects. Oral intermediate exposure, 6 mg/kg/day, based on hepatic effects [www.atsdr.cdc.gov/mrls.html] (142). Last revised 6/95.

B. Inhalation
Not available.

*Continued on next page*
Di-N-octyl phthalate (DnOP)

A. Oral/Ingestion

U.S. ATSDR Minimal Risk Level (MRL): Oral acute exposure, 3 mg/kg/day, based on hepatic effects. Oral intermediate exposure, 0.4 mg/kg/day, based on hepatic effects (www.atsdr.cdc.gov/mrls.html) (142). Last revised 9/97.

B. Inhalation

Not available.

VII. U.S. FEDERAL REGULATORY INFORMATION

- The U.S. EPA IRIS is currently reviewing toxicity reference values for BBP, DBP, and DEHP (49).
- There are no U.S. regulations on the use of phthalates in children’s toys, although many manufacturers voluntarily stopped using phthalates in teethers and rattles in 1999, and the use of phthalates in nipples was voluntarily discontinued beginning in 1986 (1, 6, 122).
- DBP, DEHP, and DMP are included on the list of 188 hazardous air pollutants (HAPs) listed under section 112(b) of the 1990 Clean Air Act Amendments and are regulated from more than 170 industrial source categories (147).
- There are 10 phthalates are listed by the U.S. EPA as inert ingredients in pesticides, each listed on one of four lists ranked by level of toxicological concern and amount of toxicological information available (136). DEP was recently moved from List 2 (Potentially Toxic Other Ingredients/High Priority for Testing Inerts) to List 4B (Other ingredients for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment) (136).
- The U.S. EPA requires reporting of quantities of certain chemicals that exceed a defined reportable quantity, and that quantity varies for different chemicals (148). Under the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 “Toxic Chemicals,” reporting of quantities of DBP, DEHP, or DMP greater than 10,000 pounds manufactured or processed, or otherwise used, is required (148). Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), quantities of releases for required reporting vary depending on the phthalate: DBP, 10 pounds; BBP and DEHP, 100 pounds; DEP, 1,000 pounds; and DMP, 5,000 pounds (148).
VIII. BACKGROUND ON CHEMICAL

A. CAS Numbers: Butyl benzyl phthalate, 85-68-7; Diethyl phthalate, 84-66-2; Dibutyl phthalate, 84-74-2; Di(2-ethylhexyl) phthalate, 117-81-7; Dimethyl terephthalate 120-61-6.

B. Physicochemical Properties: Phthalates in pure form are clear-to-yellowish liquids, some with mild odors; go to http://chem.sis.nlm.nih.gov/chemidplus/ and search for each phthalate by name or by CAS number.

C. Production: Phthalates are widely used industrial and commercial chemicals, mainly as plasticizers in polyvinyl chloride (95% of DEHP industrial use) and other polymers such as rubber, cellulose, and styrene (149). Production of DEHP was estimated to be 258 million pounds in 1994 (150), and production of all dioctyl phthalates was estimated to be 285 million pounds in 1998 (1). More recent numbers are not available because the information is considered proprietary by the chemical manufacturing companies (1).

D. Uses: Phthalates or phthalic esters are a group of compounds used as plasticizers in polyvinyl chloride and other polymers, as well as for other polymers (1-6). Many packaging materials contain phthalates, including food and beverage items and some medical products. They are widely used compounds found in a diverse range of products, including: cosmetics, pesticides (as carriers), soaps and detergents, inks, lacquers, lubricating oils, adhesives, photographic film, wire and cable, toys, toothbrushes, and defoaming agents. For phthalates listed in TRI, total reported releases and disposals in 2004 were: DEHP over 840,000 pounds; DBP over 177,000 pounds; and DMP over 414,000 pounds. Note these reported releases and disposals should be considered a minimum estimate because only certain types of facilities are required to report (150).

E. Environmental Fate: Phthalates can leach from plastic packaging into the food and beverage items they surround (1-6). In the environment, phthalates are found largely as a result of industrial releases. DEHP and the other phthalates can strongly adsorb to soils and sediments and rarely leaches into groundwater or evaporates (1-6). In the air, phthalates are fairly stable and can be carried long distances. When released into water, phthalates can degrade somewhat quickly; for example, DEHP has a half-life of two to three weeks in water. DEHP can bioconcentrate in aquatic systems, although not all phthalates bioconcentrate.

F. Synonyms and Trade Names: (for a more complete list, go to http://chem.sis.nlm.nih.gov/chemidplus/ and search for each phthalate by name or by CAS number)

- Butylbenzyl phthalate: Benzyl butyl phthalate; benzyl butylphthalate; benzyl n-butyl phthalate; butyl phenylmethyl 1,2-benzenedicarboxylate; CCRIS 104; Caswell No. 125G; EINECS 201-622-7; HSDB 2107; NCI-C54375; NSC 71001; Palatinol BB; Phthalic acid, benzyl butyl ester; Santicizer 160; Sicol; Sicol 160; Unimoll BB; n-Butyl benzyl phthalate, and others.

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Di(2-ethylhexyl)phthalate: DEHP; DOP; bis(2-Ethylhexyl) phthalate; Dioctyl Phthalate; 1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester; Octoil; Ethyl hexyl phthalate; 2-Ethylhexyl phthalate; bis-(2-ethylhexyl) 1,2-benzenedicarboxylate; octyl phthalate; phthalic acid dioctyl ester; BEHP; bisoflex 81; bisoflex dop; compound 889; DAF 68; ergoplast fdo; eviplast 80; eviplast 81; fleximel; flexol dop; flexol plasticizer dop; good-rite gp 264; hatcol dop; hercoflex 260; kodaflex dop; mollan o; nuoplaz dop; palatinol ah; pitman px-138; platinol ah; platinol dop; rc plasticizer dop; reomol dop; reomol d 79p; sicol 150; staflex dop; truflex dop; vestinol ah; vinicizer 80; witcizer 312; Benzenedicarboxylic acid, bis(2-ethylhexyl) ester; Union carbide flexol 380; bis (2-Ethylexyl) Phthalate; Bis(2-Ethylhexyl) Phthalate (DEHP); Bis(2-Ethylhexyl) Phthalate (Dioctyl phthalate), and others.

Diethyl phthalate: Ethyl phthalate; DEP; 1,2-benzenedicarboxylic acid diethyl ester; diethyl o-phthalate; anozol; estol 1550; neantine; palatinol a; phthalol; placidol e; solvanol; Benzenedicarboxylic acid, diethyl ester; and others.

Di-n-butyl phthalate: DBP; Di-n-Butyl Phthalate; n-Butyl phthalate; 1,2-Benzenedicarboxylic acid dibutyl ester; Phthalic acid dibutyl ester; o-benzenedicarboxylic acid, dibutyl ester; benzene-o-dicarboxylic acid di-n-butyl ester; dibutyl 1,2-benzenedicarboxylate; celluflex dbp; Elaol; hexaplas m/b; palatinol c; polycizer dbp; PX 104; staflex dbp; witcizer 300; Araldite 502; benzenedicarboxylic acid, dibutyl ester; dibutyl o-Phthalate; and others.

Dimethyl phthalate: DMP; 1,2-benzenedicarboxylic acid; dimethyl ester; dimethyl 1,2-benzenedicarboxylate; dimethyl benzene-o-dicarboxylate; dimethyl phthalate; methyl phthalate; phthalic acid; dimethyl ester; and others.

Additional information on phthalates is available in the TEACH Database for Phthalates, and at the following Web sites:

www.epa.gov/ost/drinking/standards/dwstandards.pdf
www.epa.gov/safewater/dwh/c-soc.html
http://cerhr.niehs.nih.gov/chemicals/

Supporting references and summaries are provided in the TEACH Database at http://epa.gov/teach/. Last revised 10/10/2007: includes research articles through 2005, and other information through 2006.
REFERENCES


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Chemical Summary, Phthalates (continued)


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