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CONSUMER PRODUCT SAFETY COMMISSION
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Memorandum

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SUBJECT : CPSC Staff Toxicity Review of 17 Phthalates for
Consideration by the Chronic Hazard Advisory Panel - 2010¹

This memo provides the U.S. Consumer Product Safety Commission's (CPSC's) Health Sciences staff assessment of the potential toxicity associated with 17 of the less commonly used phthalate ester compounds, for consideration by the phthalate Chronic Hazard Advisory Panel.

CPSC staff assesses a product's potential health effects to consumers under the Federal Hazardous Substances Act (FHSA). The FHSA is risk-based. To be considered a "hazardous substance" under the FHSA, a consumer product must satisfy a two-part definition. 15 USC 1262 (f)(1)(A). First, it must be toxic under the FHSA, or present one of the other hazards enumerated in the statute. Second, it must have the potential to cause "substantial illness or injury during or as a result of reasonably foreseeable handling or use." Therefore, exposure and risk must be considered in addition to toxicity when assessing potential hazards under the FHSA (CPSC 1992; summarized at 16 C.F.R. 1500.135).

The FHSA addresses both acute and chronic hazards. While the FHSA does not require manufacturers to perform any specific battery of toxicological tests to assess the potential risk of chronic health hazards, the manufacturer is required to label a product appropriately according to the requirements of the FHSA. The first step in the risk assessment process is hazard identification, that is, a review of the available toxicity data for the chemical under consideration and a determination of whether the chemical is considered "toxic" under the FHSA. Chronic toxicity data (including carcinogenicity, neurotoxicity, and reproductive and developmental toxicity) are assessed by the CPSC staff using guidelines issued by the Commission (CPSC 1992). If it is concluded that a substance is toxic under the FHSA due to chronic toxicity, then a quantitative assessment of exposure and risk is performed to evaluate whether the chemical may be considered a "hazardous substance" under the FHSA. This memo represents the first parts of the risk assessment process, that is, the hazard identification and dose-response steps.

¹ These comments are those of the CPSC staff and have not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

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INTRODUCTION

Dialkyl *ortho*-phthalates (o-DAP's) are a class of commercial chemicals that are used primarily as plasticizers for polyvinyl chloride (PVC) and as solvents. The general structure is a diester of 1,2-dicarboxy-benzene (Figure 1). The two alkyl groups (R and R') may be similar or dissimilar; they may be branched or linear; and they may contain aromatic substituents or other functional groups. The o-DAPs are of particular interest due to widespread human exposure and the observation that certain o-DAPs induce reproductive and developmental health effects in animals. In addition, certain developmental effects of o-DAPs are believed to be additive. Thus, the effects of exposure to multiple phthalates may be greater than the effects of the individual compounds.

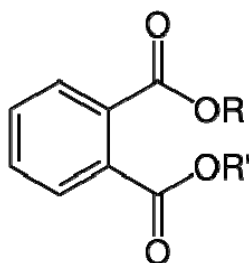


Figure 1: Dialkyl *ortho*-Phthalate

The phthalate esters are divided into three subcategories based on their physicochemical and toxicological properties: (1) low molecular weight phthalates, (2) transitional phthalates, and (3) high molecular weight phthalates. Low molecular weight phthalates are produced from alcohols with straight-chain carbon backbones of $\leq C_3$. The medium weight or transitional phthalates group comprises o-DAPs containing >10 percent molecules derived from alcohols with alkyl chains of four, five, or six carbons (U.S. EPA 2001). In general, these have greater potential toxicity to mammals, reproductive and developmental toxicity in particular, when compared with most high and low molecular weight phthalates (U.S. EPA 2001; Heindel et al. 1989; Foster et al. 1980). Compared to high molecular weight phthalates, these transitional phthalates tend to have higher water solubility, volatility, propensity to migrate, and dermal absorption (U.S. EPA 2001; Elsisi et al. 1989). Finally, high molecular weight phthalate esters (HMWPE) are derived from alcohols with seven or more carbon atoms, or a ring structure. The HMWPEs are used mainly as plasticizers for PVC, and other plastics like polyvinyl acetate and polyurethane, or in elastomers, coatings, adhesives, and sealants. High molecular weight plasticizers are desirable in manufacturing when low chemical migration or volatility is desired, such as in automobile interiors (e.g., upholstery), electrical insulation, vinyl flooring, home furnishings, toys, garden hoses, carpet backing, footwear, rainwear, and stationery (CPSC 2010). Other PVC applications of HMWPEs in general include furniture and wall coverings, coil coatings, pool liners, roofing membranes, and coated fabrics. Non-PVC applications of HMWPEs include lubricating oil, thermoplastic polymers, rubbers and selected paints, and adhesives (NICNAS 2007).

The general population may be exposed to phthalate esters via dermal, oral, or inhalation contact with consumer products containing them. Exposure to HMWPEs via offgassing from products containing these compounds is expected to be relatively low, based on their low volatility.

Nonetheless, HMWPEs have been detected in household dust. The general population is also exposed to some phthalate esters in food. At workplaces where plastics are produced, or where a phthalate compound is used as a plasticizer, occupational exposure to that phthalate may occur through inhalation of aerosols or dermal contact.


The U.S. Consumer Product Safety Commission (CPSC) staff has written hazard summaries for six phthalates outlined in the Consumer Product Safety Improvement Act (CPSIA; 2008): butyl benzyl, dibutyl, di (2-ethylhexyl), di *n*-octyl, disononyl, and diisodecyl phthalate (BBP, DBP, DEHP, DnOP, DINP, and DIDP, respectively). Five sources of information were used by CPSC staff to determine which other phthalates require investigation: (1) a TOXNET database search for publications, (2) U.S. phthalate production and consumption estimates, (3) listing as a High Production Volume (HPV) chemical by the U.S. EPA, (4) information on phthalates actively monitored in biological media, (and 5) hazard, exposure, or risk reports written by other agencies.

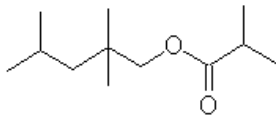

The purpose of this document is to review the current toxicity datasets for 17 of these less commonly used phthalate esters (listed in Table 1). Six of these compounds fall into the transitional phthalates group: (1) diamyl phthalate, (2) dihexyl phthalate, (3) branched and linear dihexyl phthalate, (4) branched and linear diheptyl phthalate, (5) di-C6-8-branched phthalate, C7-rich, and (6) branched and linear heptyl undecyl phthalate. The remaining 10 compounds are HMWPEs. Eight of the 17 compounds reviewed here contain mixtures of *o*-DAPs with different chain lengths, such as di-C6-10 alkyl phthalates. One of the 17 phthalates reviewed here is a pure branched compound (1,2-benzenedicarboxylic acid, 2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl phenylmethyl ester); one of the 17 is a mixture of branched isomers (di-C11-14-branched alkyl phthalates, C13-rich); four of the 17 are linear diesters (diamyl, dihexyl, dinonyl, and didecyl phthalate); and the rest of the 17 are mixtures of branched and linear isomers.

This assessment was prepared from peer-reviewed literature, including review articles, and unpublished studies carried out by industry. The literature search was executed in July–August 2010, and included online databases such as Toxnet (which indexes databases including ChemIDPlus, DART, HSDB, and Toline), TSCATS, and IPCS INCHEM. Toxicological reviews and robust summaries from groups such as the Australian Government (National Industrial Chemicals Notification and Assessment Scheme, NICNAS), the Center for the Evaluation of Research on Human Reproduction (CERHR), the European Chemicals Bureau (ECB), and the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) program are referenced throughout this report.

There were significant data gaps for many of the compounds presented here. Based on structure activity relationships (SAR), many of these gaps were able to be filled in with the available literature on similar compounds found in this report, or on the more common and more extensively studied compounds like diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), and di-*n*-octyl phthalate (DnOP). Some of these other phthalates were reviewed previously by CPSC staff (Babich and Osterhout 2010; Carlson 2010; and Osterhout 2010).

The remainder of this report describes toxicity, use, and exposure data identified for each of the 17 phthalate diesters listed below in Table 1. Compounds are divided by section, and descriptions of data are followed by summary tables for each compound.

Table 1: Phthalate Compounds Reviewed in this Document				
Chemical Name	CAS Number	Molecular Formula	MW	R-Group Structure
1,2-Benzenedicarboxylic acid, dipentyl ester (Diamyl phthalate)	131-18-0	C ₁₈ H ₂₆ O ₄	306.4	R ₁ = R ₂ = C ₅ H ₁₁
1,2-Benzenedicarboxylic acid, dihexyl ester	84-75-3	C ₂₀ H ₃₀ O ₄	334.5	R ₁ = R ₂ = C ₆ H ₁₃
1,2-Benzenedicarboxylic acid, dinonyl ester, branched and linear	68515-45-7	C ₂₆ H ₄₂ O ₄	418.6	R ₁ = R ₂ = C ₉ H ₁₉
1,2-Benzenedicarboxylic acid, didecyl ester	84-77-5	C ₂₈ H ₄₆ O ₄	446.7	R ₁ = R ₂ = C ₁₀ H ₂₁
1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear	68515-50-4	C ₂₀ H ₃₀ O ₄	334.5	R ₁ = R ₂ = C ₆ H ₁₃ (branched or linear)
1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich	68515-47-9	C ₃₄ H ₅₈ O ₄ (based on C13)	475-559	R ₁ or R ₂ = C ₁₁ H ₂₃ or C ₁₂ H ₂₅ or C ₁₃ H ₂₇ or C ₁₄ H ₂₉
1,2-Benzenedicarboxylic acid, dinonyl ester	84-76-4	C ₂₆ H ₄₂ O ₄	418.6	R ₁ = R ₂ = C ₉ H ₁₉
1,2-Benzenedicarboxylic acid, di-C6-10 alkyl phthalates	68515-51-5	C ₂₇ H ₄₄ O ₄ (Based on one C6 and one C10)	334.5 – 446.7	R ₁ or R ₂ = C ₆ H ₁₃ or C ₇ H ₁₅ or C ₈ H ₁₇ or C ₉ H ₁₉ or C ₁₀ H ₂₁
1,2-Benzenedicarboxylic acid, di-C7-9-branched and linear alkyl esters	68515-41-3	C ₂₄ H ₃₈ O ₄ (based on C8 length)	362.5 – 418.6	R ₁ or R ₂ = C ₇ H ₁₅ or C ₈ H ₁₇ or C ₉ H ₁₉ (branched or linear)
1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters	68515-40-2	C ₂₁ H ₂₅ O ₄ (based on C7 length)	341.4 – 369.5	R ₁ =  R ₂ = C ₇ H ₁₅ or C ₈ H ₁₇ or C ₉ H ₁₉ (branched or linear)

1,2-Benzenedicarboxylic acid, diundecyl ester, branched and linear	85507-79-5	C ₃₀ H ₅₀ O ₄	474.7	R ₁ = R ₂ = C ₁₁ H ₂₃ (branched or linear)
1,2- Benzenedicarboxylic acid, 2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl phenylmethyl ester	16883-83-3	C ₂₇ H ₃₄ O ₆	454.6	<p>R₁ =</p>  <p>R₂ =</p> 
1,2-Benzenedicarboxylic acid, diheptyl ester, branched and linear	68515-44-6	C ₂₂ H ₃₄ O ₄	362.5	R ₁ = R ₂ = C ₇ H ₁₅ (branched or linear)
1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich	71888-89-6	C ₂₂ H ₃₄ O ₄ (based on C7/C7)	334 - 391	R ₁ or R ₂ = C ₆ H ₁₃ or C ₇ H ₁₅ or C ₈ H ₁₇ (branched only)
1,2-Benzenedicarboxylic acid, heptyl undecyl ester, branched and linear	111381-90-9	C ₂₆ H ₄₂ O ₄ (based on C7/C11)	362.5 – 474.7	R ₁ or R ₂ = C ₇ H ₁₅ or C ₁₁ H ₂₃ (branched or linear)
1,2-Benzenedicarboxylic acid, nonyl undecyl ester, branched and linear	111381-91-0	C ₂₈ H ₄₆ O ₄ (based on C9/C11)	418.6 – 474.7	R ₁ or R ₂ = C ₉ H ₁₉ or C ₁₁ H ₂₃ (branched or linear)
1,2-Benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters	68648-93-1	C ₂₄ H ₃₈ O ₄ (based on C6/C10)	334.5 – 446.7	R ₁ or R ₂ = C ₆ H ₁₃ or C ₈ H ₁₇ or C ₁₀ H ₂₁

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1,2-BENZENEDICARBOXYLIC ACID, DIPENTYL ESTER (CAS # 131-18-0)

1,2-Benzenedicarboxylic acid, dipentyl ester, commonly known as diamyl phthalate or dipentyl phthalate, is a linear *ortho*-phthalate diester comprising two five-carbon backbones. Diamyl phthalate is manufactured commercially by esterification of phthalic anhydride with amyl alcohol in the presence of a 1 percent concentrated sulfuric acid catalyst (HSDB 2010). The major use of this phthalate is as a plasticizer in polyvinyl chloride (PVC), including in membrane electrodes. It is also used as a solvent in personal care products, inks, dyes, nitrocellulose, and resin lacquer (HSDB 2010), and in the prevention of foam in the manufacture of glue and rubber cements (Colborn et al. 1996).

Harris et al. (1997) estimated that the European production of diamyl phthalate was “negligible” (<< 1000 tons/year). In 1990, the Inventory Update Report (IUR) listed U.S. production/importation volume of diamyl phthalate to be 10,000–500,000 pounds (U.S. EPA 2002). The most recent IUR data (from 2006) contains no reports of this phthalate being produced or imported into the United States (U.S. EPA 2006). Diamyl phthalate, therefore, does not qualify as a High Production Volume material (≥ 1 million lbs/year).

Exposure

At workplaces where plastics are produced or where diamyl phthalate is used as a plasticizer, occupational exposure to diamyl phthalate may occur through inhalation of aerosols or dermal contact (HSDB 2010). The general population may be exposed via dermal, oral, or inhalation contact with consumer products containing this compound. In addition to polyvinyl chloride, products containing diamyl phthalate include air fresheners (Cohen et al. 2007), pharmaceutical devices (Corium International 2006), personal care products, inks, dyes, rubber cement, glue nitrocellulose, and resin lacquer (HSDB 2010; Colborn 1996).

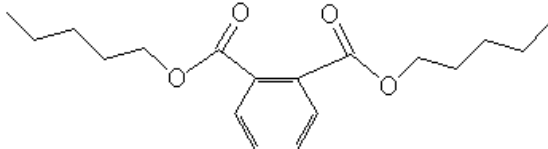
Exposure to diamyl phthalate via contact with toys is not expected to be a concern because diamyl phthalate is not commonly used as a plasticizer in toys (Chen 1998, 2002; Dreyfus 2010; DEPA 2006; Stringer et al. 2000; Sugita et al. 2001). In a year 2000 survey of 72 toys (64 of which were made of PVC) from 17 different countries, no diamyl phthalate was detected (Stringer et al. 2000). Similarly, the Danish Environmental Protection Agency measured phthalate levels in eight toys (DEPA 2006) and Sugita et al. (2001) looked at 68 toys, and neither survey found detectable diamyl phthalate.

The European Union’s Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE; 1998) used *in vitro* leachate data to estimate oral exposure of a variety of phthalates from PVC toys to teething babies. Diamyl phthalate was not detected in leachate in the two *in vitro* studies reporting this compound (detection limit for one study reported to be 256 $\mu\text{g}/\text{dm}^2$). Conservatively assuming the concentration leaching from the toy is equal to the detection limit, and using conservative model parameters,² the model predicts a maximum exposure of 0.8 μg diamyl phthalate/kg body weight (bw)/day.

² 6 hour exposure period, 10 cm^2 product surface area, and 8 kg body weight.

Physicochemical Properties

Some physical and chemical properties of diamyl phthalate are summarized below in Table 2.

Table 2: Physicochemical Properties of Diamyl Phthalate	
Identification	Information
Chemical Name	Diamyl phthalate
Synonyms	Di-n-pentyl phthalate; 1,2-Benzenedicarboxylic acid, dipentyl ester; Amoil; Amyl phthalate; Phthalic acid, diamyl ester; Phthalic acid, dipentyl ester
CAS Number	131-18-0
Structure	
Chemical Formula	C ₁₈ H ₂₆ O ₄
Molecular Weight	306.397
Physical State	Liquid
Color	Colorless
Melting Point	< -55°C
Boiling Point	342°C
Vapor Pressure	1.96x10 ⁻⁴ mmHg @25°C
Water Solubility	0.8 mg/L @25°C
Log K _{ow}	5.62
Flashpoint	118-180°C
Source: HSDB 2010	

Toxicokinetics

No data were identified specific to the absorption of diamyl phthalate. In a study of the toxicokinetics of a series of phthalate esters, Elsis et al. (1989) found that dermal absorption of phthalate diesters depended on several competing factors, such as lipophilicity, molecular size, and metabolism. Dermal uptake decreased with increasing side chain length beyond four carbons, and uptake decreased progressively with side chain length beyond four carbons, despite the fact that the lipophilicity increased.

Histological data from acute toxicity studies suggest that diamyl phthalate is distributed quickly. Germinal cell dissociation from the basal membrane of seminiferous tubules occurred within three hours of a single oral dose of 2000 mg/kg diamyl phthalate to the rat. After six hours, the effect was marked, and after 24 hours, vacuolation was observed in the Sertoli cell cytoplasm,

accompanied by a significant decrease in succinate dehydrogenase activity in the mitochondria (Gangoli 1982).

Following oral exposure, diamyl phthalate is rapidly metabolized *in vivo* to its corresponding monoester by nonspecific esterases in the intestinal mucosa and other tissues (Gangoli 1982). For phthalate esters in general, after formation of the monoester, there can be further hydrolysis *in vivo* to phthalic acid or the corresponding alcohol, which can be excreted or further oxidized to an aldehyde, ketone, or carboxylic acid. The monoester can also undergo glucuronidation (Wittasek and Angerer 2008).

The monoester and oxidative metabolites and conjugants of phthalate diesters are excreted in the urine and feces (Wittasek and Angerer 2008). Elsisi et al. (1989) noted that the pattern of excretion changed based on chain length. Phthalate esters with chain lengths of six carbons or less showed less fecal and more urinary excretion compared to longer chain esters.

Acute Toxicity

An oral LD₅₀ of 29600 mg/kg bw diamyl phthalate has been established in rats (Sciencelab.com 2008). No further acute systemic toxicity data were identified for diamyl phthalate in a search of the literature.

Irritation and Sensitization

No data on ocular, dermal, or respiratory irritation or sensitization of diamyl phthalate were identified in the relevant literature.

Systemic Toxicity

Nervous system

Lu et al. (2004) investigated the effects of eight phthalates, including diamyl phthalate, on the calcium signaling of acetylcholine receptors (AChRs) by using human neuroblastoma SH-SY5Y cells. AChRs serve as ion channels in neuron cells and are regulated by antagonizing and agonizing ligands. They are the site of excitatory neurotransmissions in the central and peripheral nervous systems and play an important role in learning and memory, and modulation of blood catecholamine, heart rate, and blood pressure. With varying potencies, all eight phthalates inhibited agonist-induced calcium signaling in the human nicotinic AChR. The compounds in order of strongest to weakest inhibition potency were: diamyl phthalate > butyl benzyl phthalate (BBP) > di-n-butyl phthalate (DBP) > dicyclohexyl phthalate (DCHP) > di-n-hexyl phthalate (DnHP) > di-(2-ethyl hexyl) phthalate (DEHP) > di-n-propyl phthalate (DPrP) > diethyl phthalate (DEP). Dialkyl group carbon numbers of C4 or C5 were associated with the strongest inhibition; carbon numbers less than four and greater than five were less potent. At concentrations as low as 0.1 μ M, diamyl phthalate, DBP, BBP, DCHP and DnHP significantly inhibited the calcium signaling of human nicotinic AChR. The IC₅₀ (concentration at which calcium signaling was inhibited by 50 percent) for diamyl phthalate was 0.32 μ M for human nicotinic AChR. A similar trend had been noted previously in bovine chromaffin cells, but IC₅₀ values in bovine nicotinic AChR were higher (3.94 μ M in diamyl phthalate) (Lu et al. 2004).

Liver

Hepatic peroxisome proliferation was measured *in vitro* in the presence of multiple phthalate monoesters. Gray et al. (1983) assessed peroxisome proliferation using electron microscopy plus three biomarkers: carnitine palmitoyltransferase, cyanide-insensitive palmitoyl-CoA oxidation, and carnitine acetyltransferase. Rat hepatocytes were incubated with 0.2 mM phthalate monoester for 48 hours. In the presence of mono-amyl phthalate, carnitine palmitoyltransferase activity was approximately 150 percent that of controls, and carnitine acyltransferase activity and cyanide-insensitive palmitoyl-CoA oxidation were 545 percent and approximately 260 percent, respectively, that of control cells. Diamyl phthalate also significantly increased carnitine acyltransferase activity (416 percent), although pentanol did not. Despite these biochemical data, mono-amyl phthalate did not produce increased numbers of peroxisomes as measured through electron microscopy. Carnitine acyltransferase, while often associated with peroxisomal changes, can be activated by changes in mitochondria as well. Because there was no structural evidence of peroxisome proliferation, study authors posited mitochondrial changes were responsible for the increased activity of hepatic carnitine acyltransferase in the presence of diamyl phthalate (Gray et al. 1983).

Endocrine System

Diamyl phthalate concentrations ranging from 10^{-3} M to 5×10^{-7} M did not induce estrogenic activity in the recombinant yeast screen (Harris et al. 1997), and the ESCREEN assay (Soto et al. 1995), which measures the estrogen-induced increase in the number of human breast MCF-7 cells.

Reproductive and Developmental Toxicity

Testicular atrophy induced by diamyl phthalate exposure has been well documented in the literature. *In vivo* and *in vitro* studies indicate that seminiferous tubules and Sertoli cells, in particular, are the primary site of diamyl phthalate toxicity in the testes (Gangolli 1982; Creasy et al. 1983; Granholm et al. 1992; Jones et al. 1993; Gray and Gangolli 1986). Within six hours of a single oral dose of 2000 mg/kg diamyl phthalate to the rat, germinal cells dissociated from the basal membrane of seminiferous tubules (Creasy et al. 1983). After 24 hours, vacuolation was observed in the Sertoli cell cytoplasm and succinate dehydrogenase activity in mitochondria was significantly decreased (Gangolli 1982). Two to four days of daily phthalate treatment resulted in a gradual depletion of germinal cells from all tubules, leaving a few necrotic spermatocytes and only occasional normal spermatogonia (Creasy et al. 1983). Likewise, cultured seminiferous tubules exposed to monoamyl phthalate *in vitro* showed a dose-dependent detachment of germ cells from the basal membrane (Gangolli 1982). At monoester concentrations of 30, 100, 300, or 1000 μ M, the percent of detached germ cells after 48 hours compared to controls was 179 percent, 223 percent, 257 percent, and 474 percent, respectively. No significant dissociation of germ cells occurred at 10 μ M diamyl phthalate. The monoesters of phthalates that did *not* induce testicular injury *in vivo* did not cause germ cell detachment in this study (Gangolli 1982).

Granholm et al. (1992) observed that Sertoli cell damage is concomitant with leukocyte infiltration into the testicular interstitium. The rat testis constitutively produces a lymphocyte activating factor (LAF) originating from Sertoli cells. Upon exposure to 2200 mg/kg bw diamyl phthalate, testicular LAF activity increased significantly in rats within three hours. The increase

was maximal 9 to 12 hours after exposure, and had decreased toward the control level after 24 hours. The increased activity was shown to be due, in part, to the induction of a novel LAF.

Other biochemical changes that have been observed in testis functioning in the presence of diamyl phthalate include a reduction in the production of fluid in the rete testis (a network of channels in the seminiferous tubules) and androgen-binding protein (Gangolli 1982).

In a study of the relative reproductive toxicity of eight phthalate esters to rats, diamyl phthalate caused the most severe testicular atrophy (Foster et al. 1980). Rats received 2100 mg/kg bw/day diamyl phthalate for four days. Relative testis weights were 56.6 percent of control weights ($p < 0.001$). Dibutyl and di-n-hexyl phthalate reduced testes weight to 66.9 percent and 64.8 percent, respectively, while the remaining six phthalates did not significantly change testis weight. An accompanying increase in urinary zinc was observed and attributed to the diamyl phthalate-induced decrease in membrane bound zinc associated with spermatids. Concomitant changes in urinary zinc levels were not observed in rats given phthalate compounds *not* associated with testicular injury (Foster et al. 1980).

Treatment of Sprague Dawley rats via gavage with 7.2 mmol/kg bw diamyl phthalate (~2200 mg/kg bw) was shown to decrease testicular cytochrome P-450, cytochrome P-450 dependent microsomal steroidogenic enzymes (17 alpha-hydroxylase, 17-20 lyase) and the maximal binding of a natural substrate (progesterone) to microsomes of the testes. The study authors concluded that diamyl phthalate has a direct effect on cytochrome P-450-dependent steroid production, which may be directly responsible for the toxic effects on testicular structure and function. Treatment of animals with diethyl phthalate, a compound that is not associated with testicular atrophy, produced no significant changes in any of the parameters measured. There was no effect of diamyl phthalate on hepatic cytochrome P-450 content (Foster et al. 1983).

A tandem *in vitro/in vivo* study evaluated the toxicity of phthalate esters, including mono- and diamyl phthalate, to Leydig cells. *In vivo*, three rats were exposed to diamyl phthalate at 2000 mg/kg bw/day by gavage for two days, and then sacrificed after 24 hours. Diamyl phthalate did not affect the structure of Leydig cells *in vivo*, which, in other diester phthalates, was characterized by mitochondrial swelling. In the *in vitro* portion, 1000 μ M monoamyl phthalate had no effect on rat Leydig cells after 2 to 3 hours of exposure. The phthalate monoesters evoking an adverse response *in vitro* increased the luteinizing hormone (LH)-stimulated secretion of testosterone from Leydig cells and significantly altered these cells' ultrastructural integrity. The absence of toxicity of the amyl phthalate esters to Leydig structure and function suggests that their mode of toxic action on the male rat reproductive system is via Sertoli cells only. Based on these results, diamyl phthalate is expected to directly affect germ cell functioning, but not androgen supply (Jones et al. 1993).

Androgen binding protein (ABP) was measured in the serum of diamyl phthalate-treated rats as a potential index of germinal epithelial damage and hence, of Sertoli cell toxicity (Lindstrom et al. 1988). Fischer 344 rats received single gavage doses of 0, 250, 1000, or 2000 mg/kg bw diamyl phthalate. Each week, for 10 weeks, 10 rats were sacrificed and examined for evidence of epithelial damage. In high-dose rats, serum ABP values more than doubled within two days of exposure, remained significantly elevated for 3 weeks, then fell and remained significantly

below control values through the end of the experiment. Nearly all (95 percent) high-dose rats showed more than half of their seminiferous tubules degenerated, and demonstrated decreased epididymal sperm density, reduced testicular and epididymal weight, and up to 23 percent abnormal sperm morphology. Rats receiving 1000 mg/kg bw diamyl phthalate showed decreased epididymal sperm density, and their epididymal and testicular weights were consistently, although not always, significantly lower than controls. ABP levels were initially higher than control levels, but returned to normal levels by week 2. In rats receiving 250 mg/kg bw, the only significant change was a decrease in the epididymal sperm density on weeks 4, 5, 6, 7, and 9. ABP was determined to be a peripheral index of Sertoli cell toxicity, at best. Diamyl phthalate treatment did not produce any significant effect on body, liver, kidney, prostate, or seminal vesicle weight at any dose (Lindstrom et al. 1988).

Lindstrom et al. (1988) used the exposure regime described above to measure the effect of diamyl phthalate on fertility. Treated males were mated with untreated females at 3, 6, and 10 weeks post-exposure. The percentage of high-dose rats successfully impregnating at least one female was 65 percent of controls at week 3; 15 percent at week 6; and 35 percent at week 10. The number of live fetuses per pregnant female crossed with a high-dose male was 35 percent, 43 percent, and 72 percent of controls at weeks 3, 6, and 10, respectively. Preimplantation loss in cross-matings was three times that of controls. There was no significant difference in the number of resorptions or dead fetuses (i.e., post-implantation loss) at any time. All males showed typical phthalate ester-induced testicular lesions, which did not recover within the 30-week monitoring period. There were no effects on fertility at the mid- or low- doses.

The National Toxicology Program (NTP) tested the reproductive toxicity of diamyl phthalate using the Fertility Assessment by Continuous Breeding (FACB) protocol in Swiss CD-1 mice as part of a structure-activity evaluation of a variety of phthalates. Male and female mice (20/sex/dose) received diamyl phthalate in the diet at concentrations of 0.5, 1.25, or 2.5 percent (approximately equivalent to 760, 2160, and 4800 mg/kg/day, respectively) for 7 days prior to and during a 98-day cohabitation. The reproductive NOAEL was determined to be less than 760 mg/kg/day, based on significant decreases in the proportion of fertile pair groups, number of litters per pair, number of live pups per litter, and the proportion of live births. At the two high doses, there was a complete inhibition of fertility (Heindel et al. 1989; NTP 1985).

High-dose and control males and females from the aforementioned NTP reproductive toxicity study were crossbred to determine any gender-related effects of diamyl phthalate on reproduction. During the 7-day mating period, all animals received the control diet. Results of the crossover mating experiment indicate that the effect of diamyl phthalate on fertility has a strong male and female component. The mating index was severely diminished when treated males were crossed with control females, but not vice versa. Both crossover group types were totally infertile (i.e., did not produce a single litter). These results underscore that the primary site of action for diamyl phthalate in mice is the male reproductive system, although damage to female reproduction is not absent. No histological changes were observed in female reproductive organs, indicating that infertility in the treated female x control male group was related to prenatal toxicity or fetal resorption (Heindel et al. 1989; NTP 1985).

High-dose and control mice of the parental generation were necropsied following crossover mating. In females, body weight and adjusted kidney weight were significantly lower in treated versus control mice, while adjusted liver weight was greater. The high dose of diamyl phthalate in male mice was also associated with decreased body weight, increased relative liver weight, and decreased relative testis, seminal vesicle, and epididymis weight. In addition, epididymal sperm was not detectable in treated mice (NTP 1985).

Pregnant Sprague-Dawley rats were administered 500 mg/kg/day diamyl phthalate by gavage from Gestational Days (GD) 12-19. Testes were isolated on GD 19, and anogenital distances were determined. Anogenital distances were significantly reduced in male fetuses exposed to diamyl phthalate relative to control ($p < 0.001$) (Liu et al. 2005).

Howdeshell et al. (2008) compared the reproductive toxicity of a number of individual phthalates (benzylbutyl phthalate (BBP), di(n)butyl phthalate (DBP), diethylhexyl phthalate (DEHP), diethyl phthalate (DEP), diisobutyl phthalate (DiBP) and diamyl phthalate (DAP)), as well as a mixture of those phthalates. Doses of 0, 25, 50, 100, 200, 300, 600, or 900 mg/kg/day DAP were administered by gavage on gestation days (GD) 8-18 to Sprague-Dawley rats. The number of rats per dose group were 6 (control), 5 (25 mg/kg/day), 4 (50 and 200 mg/kg/day), 3 (300 mg/kg/day), and 2 (600 and 900 mg/kg/day). The NOAEL for reproductive and maternal effects was 200 mg/kg/day DAP based on significant changes in maternal body weight gain, number of live fetuses, total resorptions, and fetal mortality. Testicular testosterone production was measured on GD 18. The effective dose which inhibited fetal testosterone production by 50 percent (ED_{50}) was calculated to be 130 mg/kg/day.

In the mixture experiment, the top dose (100 percent) included a total of 1300 mg of the five phthalates BBP, DBP, DEHP, and DiBP each at 300 mg/kg/day, plus 100 mg/kg DAP/day) and was administered at 100, 80, 60, 40, 20, 10, and 5 percent of the top dose. This dose ratio was selected based on ED_{50} values obtained from the individual phthalates study. The phthalate mixture significantly reduced GD 18 testosterone production rate at 20 percent of the top dose and greater. At 40 percent of the top dose, maternal body weight gain, as well as total resorptions and fetal mortality were significantly different from controls as a result of treatment. The authors determined that antiandrogenic phthalates exert cumulative, dose additive, inhibitory effects on fetal steroidogenesis in the rat (Howdeshell et al. 2008).

Liu et al. (2005) examined global gene expression in the testes of fetal rats exposed *in utero* to diamyl phthalate in order to identify the genes and gene networks that ultimately brought about a reduction in or absence of fertility. The expression of 391 genes was found to be significantly altered by exposure to dibutyl, di-(2-ethylhexyl), butyl benzyl, and diamyl phthalates, all of which are developmentally toxic, but not by non-developmentally toxic phthalates. Disrupted gene pathways related to testicular steroidogenesis or Sertoli cell-germ cell interactions. The former included: cholesterol transport, intracellular lipid and cholesterol homeostasis, insulin signaling, transcriptional regulation, and oxidative stress. Disrupted pathways in Sertoli cell-germ cell interactions included stem cell factor signaling, testin production, and Sertoli cell differentiation.

Genotoxicity

Monoamyl phthalate was tested for mutagenicity in *Salmonella typhimurium* tester strains TA98 and TA100, and *Escherichia coli* WP2 *try*⁻ strains *uvrA*⁺ and *uvrA*⁻ at concentrations up to 2000 µg/plate with and without metabolic activation with S-9 mix. The test compound did not cause a significant increase in reverse histidine mutations in the presence or absence of metabolic activation (Woodward et al 1986; Yoshikawa et al. 1983).

Carcinogenicity

No data on the carcinogenicity of diamyl phthalate were identified in a search of the literature.

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**Table 3: Summary of Toxicity Data for 1,2-Benzenedicarboxylic acid, Dipentyl Ester
(Diamyl Phthalate) (CAS #131-18-0)**

Organ/ System	Model	Exposure Route	Dose	Dose Duration	Endpoint	Effect	Reference
Neurological	Human neuroblastoma SH-SY5Y cells	<i>In vitro</i>	0.1-10 μ M	100 sec's before agonist	IC ₅₀ = 0.32 μ M	Suppression of calcium signaling at nicotinic acetylcholine receptors.	Lu et al. 2004
Liver	Rat hepatocytes	<i>In vitro</i>	Mono- or diamyl phthalate: 0.2 mM	48-hours	NOAEL < 0.2 mM	<u>Monoamyl phthalate</u> : \uparrow carnitine palmitoyltransferase activity; \uparrow carnitine acyltransferase activity; \uparrow cyanide-insensitive palmitoyl-CoA oxidation. <u>Diamyl phthalate</u> : \uparrow carnitine acyltransferase activity	Gray et al. 1983
Endocrine	Recombinant yeast screen	<i>In vitro</i>	10 ⁻³ M - 5x10 ⁻⁷ M	(not given)	NOEL = 10 ⁻³ M	Negative for estrogenic activity	Harris et al. 1997
Endocrine	MCF-7 breast cells (ESCREEN)	<i>In vitro</i>	1.0 nM – 10 μ M	(not given)	NOEL = 10 μ M	Negative for estrogenic activity	Soto et al. 1995
Reproductive	Rat	Gavage	2000 mg/kg	Single dose	NOAEL < 2000 mg/kg	Germinal cells dissociated from basal vacuolation in Sertoli cell cytoplasm; \downarrow mitochondrial succinate dehydrogenase activity in membrane of seminiferous tubules	Creasy et al. 1983; Gangolli 1982
Reproductive	Rat seminiferous tubules	<i>In vitro</i>	<u>Monoamyl phthalate</u> : 10, 30, 100, 300, or 1000 μ M	(not given)	NOAEL = 10 μ M monoamyl phthalate	Dose-dependent detachment of germ cells from basal membrane	Gangolli 1982
Reproductive	Rat	Gavage	2200 mg/kg bw	Single dose	NOAEL < 2200 mg/kg bw	\uparrow testicular LAF activity	Granholm et al. 1992
Reproductive	Rat	Gavage	2100 mg/kg bw/day	4 days	NOAEL < 2100 mg/kg bw/day	\downarrow relative testis wts; \uparrow urinary zinc	Foster et al. 1980

Reproductive	Sprague-Dawley rat (male)	Gavage	7.2 mmol/kg bw/day (~2200 mg/kg bw/day)	1–4 days	NOAEL <2200 mg/kg bw/day	↓ testicular cytochrome P-450, ↓ cytochrome P-450 dependent microsomal steroidogenic enzymes (17 alpha-hydroxylase, 17-20 lyase); ↓ maximal binding progesterone to microsomes in testes	Foster et al. 1983
Reproductive	Wistar rats (male)/ Rat Leydig cells	Gavage/ <i>In vitro</i>	2000 mg/kg/day 1000 µM monoamyl phthalate	In vivo: 2 days In vitro: 2–3 hrs	NOAEL = 2000 mg/kg/day (in vivo); 1000 µM (in vitro)	No effects on Leydig cell structure <i>in vivo</i> or <i>in vitro</i> .	Jones et al. 1993
Reproductive	Fischer 344 rat	Gavage	0, 250, 1000, or 2000 mg/kg bw	Single dose followed by 1–10 weeks of recovery	NOAEL = 250 mg/kg bw	<u>2000 mg/kg bw</u> : ↑ then ↓ ABP; degeneration of seminiferous tubules; ↓ epididymal sperm density; ↓ testicular and epididymal wt; abnormal sperm morphology. <u>1000 mg/kg bw</u> : ↓ epididymal sperm density; <u>250 mg/kg bw</u> : transient decrease in epididymal sperm density.	Lindstrom et al. 1988
Reproductive	Fischer 344 rat (males)	Gavage	0, 250, 1000, or 2000 mg/kg bw	Single dose followed by mating at 3, 6, and 10 weeks	NOAEL = 1000 mg/kg/day	↓ successful matings; ↓ live fetuses/pregnant female; testicular lesions in males of parental generation	Lindstrom et al. 1988

Reproductive	Swiss CD-1 mice (male and female)	Dietary	0,760, 2160, 4800 mg/kg/day	7 days prior to and during a 98-day cohabitation followed by crossover mating with some control x high-dose animals	NOAEL _{reproductive} <760 mg/kg/day NOAEL _{systemic} <4800 mg/kg/day	<p>↓ Fertile pair groups, litters/pair, live pups/litter, proportion live births. <u>2160, 4800 mg/kg/day:</u> Infertility</p> <p>Crossover mating: ↓ mating index when treated males were crossed with control females, but not vice versa. All groups infertile.</p> <p><u>At 4800 mg/kg/day</u> (no other doses examined for systemic effects): ↓ body wt and adjusted kidney wt (F); ↓ body wt (M), ↑ relative liver wt (M), relative testis wt, seminal vesicle wt, and epididymis wt., absence of epididymal sperm.</p>	Heindel et al. 1989; NTP 1985
Reproductive	Sprague-Dawley rats	Gavage	0, 25, 50, 100, 200, 300, 600, or 900 mg/kg/day	GD 8-18	NOAEL _{reproductive} = NOAEL _{maternal} = 200 mg/kg/day	<p><u>At 300 mg/kg/day and higher:</u> ↓ Maternal body weight gain, ↓ no. live fetuses, ↑ total resorptions, ↑ fetal mortality</p>	Howdeshell et al. 2008
Developmental	Sprague-Dawley rats	Gavage	500 mg/kg/day	GD 12-19	NOAEL <500 mg/kg/day	↓ Anogenital distance in male fetuses	Liu et al. 2005

1,2-BENZENEDICARBOXYLIC ACID, DIHEXYL ESTER (CAS #84-75-3)

1,2-Benzenedicarboxylic acid, dihexyl ester (di-n-hexyl phthalate; CAS #84-75-3), a linear *ortho*-phthalate diester comprising two six-carbon backbones, is considered a medium-weight, or transitional phthalate ester. Di-n-hexyl phthalate (DnHP) is manufactured commercially by the esterification of phthalic anhydride with hexanol in the presence of a catalyst (HSDB 2010). According to the U.S. Environmental Protection Agency's Inventory Update Reporting program, the DnHP manufactured or imported into the United States was between 500,000 and one million pounds in 1985; 10,000–500,000 pounds in the years 1989, 1993, and 1997; one million to ten million pounds in 2001, and 500,000 to one million pounds in 2005 (U.S. EPA 2002; U.S. EPA 2006a). DnHP is produced primarily to be a component of other industrially important phthalates such as diisohexyl phthalate (up to 25 percent) and C6-10 phthalates (up to 1 percent) (CERHR 2003). The National Toxicology Program's (NTP) Center for Evaluation of Risks to Human Reproductive (CERHR 2003) Phthalates Expert Panel estimated that up to 500 tons could be consumed annually as a component of other phthalates.

DnHP is used to make plastisols intended for automobile parts and dip molded products. As a plasticizer in PVC, cellulose esters, and other polymers, DnHP may be found in flooring, canvas tarps, notebook covers, traffic cones, weather stripping, automobile air filters and battery covers, and shoes (CERHR 2003). DnHP is also found in dip molded products such as tool handles or dishwasher baskets, flooring, vinyl gloves, flea collars, and conveyor belts used in food processing. Neither DnHP nor DnHP-containing compounds are used in medical devices. No studies were identified that documented the detection of DnHP-containing compounds in children's toys (CERHR 2003).

Exposure

In the 1981–1983 National Occupational Exposure Survey, NIOSH estimated 7149 workers (of which 1974 were female) were exposed to dihexyl phthalate (HSDB 2010). The American Chemistry Council (then the Chemical Manufacturers Association) estimated human exposure to phthalates at workplaces where phthalates or flexible PVC is produced. Using a 10 m³/day inhalation rate and a 70 kg default body weight, ambient air levels of phthalates are predicted to be <1 mg/m³ for employees working in phthalate production, and <2 mg/m³ for those working in flexible PVC manufacturing (CMA 1999).

The general population may be exposed via dermal, oral, or inhalation contact with consumer products, drinking water, or food. DnHP can leach from plastic consumer goods during their processing, use, or disposal (CERHR 2003). Oral exposure is possible by way of food packaging; DnHP is approved as an indirect food additive, as a component of adhesives in food packaging under 21 CFR §175.105. Surveys have indicated the presence of DnHP in carcass meat, poultry, eggs, and baby formula, although no quantification of this contamination or the resulting human exposure was identified. In one European study, DnHP in milk (breast and commercial), cream, nuts, and baby food was below the detection limit of 0.01 mg/kg (Pfordt and Bruns-Weller 1999). Another source of DnHP consumer exposure is via flooring tile, which one study found contained 0.03 mg/kg DnHP (as cited in CERHR 2003). There was no documented detection of DnHP in children's toys identified in the literature search. In a survey

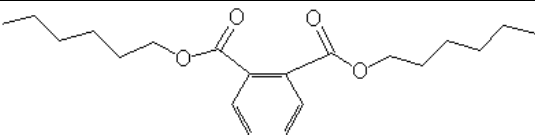
of 72 toys (64 of which were made of PVC) from 17 different countries, no dihexyl phthalate was detected (Stringer et al. 2000).

Dermal exposure to DnHP from handling plastic products is possible, but absorption through skin is relatively slow; for example, >80% of a 5-8 mg/cm² dose remained in the area of application on rats after 6 days (Elsisi et al. 1989). An *in vitro* study of other phthalates suggests that the absorption rate for human skin is even lower (Scott et al. 1987). For more details on dermal absorption, see the forthcoming section on toxicokinetics.

The American Chemistry Council predicted that consumer exposure to DnHP was less than the 3–30 µg/kg bw/day exposure estimated for di-(2-ethylhexyl) phthalate (DEHP). The prediction was based on a comparison of production volumes, consumption rates, and physicochemical properties of the two compounds (CMA 1999).

Physicochemical Properties

Names and synonyms, registry numbers, molecular structure, and other physicochemical characteristics of dihexyl phthalate are summarized below in Table 4.

Table 4: Physicochemical Properties of 1,2-Benzenedicarboxylic Acid, Dihexyl Ester	
Identification	Information
Chemical Name	Dihexyl phthalate
Synonyms	Di-n-hexyl phthalate; Di-n-hexylphthalate; 1,2-Benzenedicarboxylic acid, dihexyl ester; 1,2-Benzenedioic acid dihexyl ester; Dihexyl 1,2-benzenedicarboxylate; Bis(n-hexyl) phthalate; Hexyl phthalate, 1,2-; N-Dihexyl phthalate; Phthalic acid, dihexyl ester; 1,2-Benzenedicarboxylic acid, 1,2-dihexyl ester; DnHP
CAS Number	84-75-3
Structure	
Chemical Formula	C20-H30-O4
Molecular Weight	334.45
Physical State	Oily liquid
Color	Clear
Melting Point	< -58°C
Boiling Point	210°C
Vapor Pressure	1.40x10 ⁻⁵ mmHg @25°C
Water Solubility	0.05 mg/L @25°C
Log K _{ow}	6.82
Flashpoint	193°C

Toxicokinetics

This section describes the dermal toxicokinetics of DnHP in rats. No inhalation or oral toxicokinetic data were identified for DnHP.

Absorption

The dermal absorption of ^{14}C -labeled di-n-hexyl phthalate was quantified for seven days following a $5\text{--}8\text{ mg/cm}^2$ ($30\text{--}40\text{ mg/kg}$) dose was applied to the clipped back of male F344 rats. The absorption of DnHP was calculated as an index of the excreted fraction. Less than 6 percent of the dihexyl phthalate dose was excreted in 48 hours and between days 2 and 6; about 3 percent of the dose was excreted per day. Urine was the major route of excretion. Most of the unexcreted dose remained in the area of application. After seven days, the percentage dose that remained in the body was minimal and showed no specific tissue distribution. The data in this study also show that the structure of the phthalate diester determines the degree of dermal absorption, with shorter chain compounds having the highest degree of absorption (Elsisi et al. 1989).

Distribution

Elsisi et al. (1989; see absorption section above) measured the tissue distribution of DnHP seven days after a $30\text{--}40\text{ mg/kg}$ bw dermal dose. Most ($55\% \pm 3$) of the unabsorbed dose remained at the skin area of application and some ($4.0\% \pm 1$) was associated with the plastic cap used to protect the dosing site. The remaining DnHP distributed to skin ($0.6\% \pm 0.4$), muscle ($0.12\% \pm 0.04$), adipose tissue ($0.08\% \pm 0.05$), and other tissues including brain, lung, liver, spleen, small intestine, kidney, testis, spinal cord and blood ($<0.5\%$). Sixteen to 28 percent of the original dose was not recovered (Elsisi et al. 1989). Congruously, the CERHR (2003) found that dermally absorbed DnHP was widely distributed throughout the body with no tissue containing $>0.6\%$ of the applied dose.

Metabolism

For phthalate esters in general, after formation of the phthalate monoester, there can be further hydrolysis *in vivo* to phthalic acid or the corresponding alcohol, which can be excreted or further oxidized to an aldehyde, ketone, or carboxylic acid. The monoester can also undergo glucuronidation (Wittasek and Angerer 2008). n-Hexanol is a metabolite of DnHP and is known to be oxidized to the fatty acid and metabolized by the fatty acid oxidation pathway (CERHR 2003).

Excretion

The monoester and oxidative metabolites and conjugants of phthalate diesters are excreted in the urine and feces (Wittasek and Angerer 2008). As mentioned above, Elsisi et al. (1989) found that less than 6 percent of the $30\text{--}40\text{ mg/kg}$ bw dermal dose of DnHP dose excreted in 48 hours and then between days 2 and 6, about 3 percent of the dose was excreted per day, for a total of approximately 18 percent excretion of the dose in the seven day study. Urine was the major route of excretion; within the first 24 hours urine accounted for approximately 85 percent of total excretion of DnHP.

Acute Toxicity

The acute toxicity of di-n-hexyl phthalate is low via oral, dermal, and inhalation routes of exposure. Oral LD₅₀ values ranging from 29,600 to 38,900 mg/kg have been determined in rats, and a dermal LD₅₀ of 20,000 mg/kg was derived in rabbits. In an 8-hour inhalation exposure, the saturation vapor concentration was not lethal to rats (HSDB 2010).

No further acute systemic toxicity data were identified in a search of the literature.

Irritation and Sensitization

Based on a 10 point scale, where 10 represents the most severe injury, di-n-hexyl phthalate rated a score of 1 on rabbit eyes (HSDB 2010).

Systemic toxicity

In vitro and *in vivo* studies of the nonreproductive systemic toxicity of dihexyl phthalate toxicity indicate that the liver is the primary site of toxic action. Relevant effects associated with DnHP exposure include changes in liver morphology and biochemistry (CERHR 2003; Howarth et al. 2001; Mann et al. 1985). Mitchell et al. (1986) observed that the monoester of n-hexyl phthalate caused a rapid stimulation of fatty acid oxidation and triglyceride synthesis in hepatocytes, which was likely related to fat accumulation in the liver that has been associated *in vivo* with DnHP exposure. Other systemic effects documented in the literature include interference with calcium signaling.

Mann et al. (1985) examined systemic effects of DnHP (as well as DEHP and di-n-octyl phthalate) in 3, 10, or 21-day feeding studies of 4-week-old Wistar rats. A group of 12 male rats was fed a diet containing 2 percent (1,824 mg/kg bw/day) DnHP and a control group of 18 rats were fed the basal diet. Table 5 below summarizes the results of this study. DnHP treatment did not significantly change body weight gain, food intake levels, testes weight, or the gross appearance of testes, kidney, or pancreas. However, liver weight was significantly increased following 21 days of DnHP treatment, and histology and chemistry changes were observed at 3, 10, and 21-days. Centrilobular necrosis, loss of glycogen, and centrilobular fatty accumulation were observed during treatment and became more pronounced over the course of the treatment. Examination by electron microscopy revealed proliferation and dilation of smooth endoplasmic reticuli and shortening of the microvilli in bile canaliculi at 3 days, the presence of lipid droplets within hepatocytes at 10 days, and a small (statistically insignificant) increase in lysosomes and peroxisomes at 3 and 21 days, respectively. The activity of a peroxisomal proliferation marker cyanide-insensitive palmitoyl-CoA oxidase was significantly increased at levels approximately 2-fold greater than controls in rats only after 10 days of treatment. There was no change in total catalase activity, but catalase activity in the particulate fraction was significantly increased at 10 and 21 days of treatment. A significant decrease in glucose-6-phosphatase activity at 21 days of treatment was the only other effect on liver enzymes.

Overall, DEHP treatment resulted in a more pronounced increase in liver weight and increased mitotic activity compared to the other two phthalates. Less fat accumulated following treatment with DEHP, and when observed, the accumulation occurred in the midzonal and periportal zones rather than in the centrilobular region.

Table 5: Summary of Changes in the Livers of Rats Administered Diets Containing 2% w/w DnHP (Mann et al. 1985)	
Liver Morphology	
Hepatomegaly	+ (Late)
Centrilobular loss glycogen	+
Centrilobular necrosis	++
Peroxisome proliferation	+ (Late)
Smooth endoplasmic proliferation	+
Increase of inner mitochondrial matrix	-
Initial burst of mitosis	-
Liver Biochemistry	
Cyanide-insensitive palmitoyl CoA oxidation (<i>day 10</i>)	↑
α-Glycerophosphate dehydrogenase (<i>day 21</i>)	-
Glucose-6-Phosphate (<i>day 21</i>)	↓
Succinate dehydrogenase (<i>day 21</i>)	-
Catalase (<i>day 10</i>)	↑↑
(+) - denotes the relative effect versus controls (-) - denotes the absence of an effect ↑↓ - denotes a statistically significant increase or decrease, respectively, and its relative size * - % of control	

Comparing DnHP with DEHP, the latter induced peroxisome proliferation (as measured by cyanide-insensitive palmitoyl CoA oxidation) earlier in the treatment (within 3 days) and was a significantly stronger inducer compared to DnHP or DnOP (Mann et al. 1985). Howarth et al. (2001) provide further evidence of the limited potential for peroxisome proliferation in DnHP as compared to DEHP. In this study, male Wistar rats received 10,000 ppm (~920 mg/kg bw/day)³ of DEHP, DnHP, or both in the diet for 14 days. Changes in rats treated with the DEHP/DnHP mixture were very similar to those found in rats treated with only DEHP; the liver was enlarged and peroxisomal fatty acid oxidation and CYP4A1 were both induced. The DnHP-only group showed no increase in relative liver weight and no induction of peroxisomal fatty acid oxidation or CYP4A1, but did show a marked accumulation of fat in the liver, a fall in serum cholesterol, and thyroid changes indicative of hyperactivity. Thyroid hyperactivity was also observed following DEHP exposure and included reduction in thyroid follicular cell size and other morphological changes in the thyroid follicular cells, both of which are associated with an increased rate of thyroglobulin turnover, and are typical of chemicals that also induce liver glucuronyl transferases. Chemicals that cause liver peroxisome proliferation are also associated with the induction of liver glucuronyl transferases and thyroid hyperactivity. Since peroxisome

³ Based on a food factor of 0.092 kg food/kg bw/day (U.S. EPA 1988).

proliferation was observed following DEHP but not DnHP exposure, the two are assumed to be mechanistically independent (Howarth et al. 2001).

Hepatic peroxisome proliferation was measured *in vitro* in the presence of multiple phthalate monoesters. Gray et al. (1983) assessed peroxisome proliferation using three biomarkers: carnitine palmitoyltransferase, cyanide-insensitive palmitoyl-CoA oxidation, and carnitine acetyltransferase. Rat hepatocytes were incubated with 0.2 mM phthalate monoester for 48 hours. In the presence of mono-hexyl phthalate (MHP), carnitine palmitoyltransferase activity was not significantly different, but carnitine acyltransferase activity and cyanide-insensitive palmitoyl-CoA oxidation were 238 percent and approximately 160 percent, respectively, that of control cells.

Dihexyl phthalate also significantly increased carnitine acyltransferase activity (184 percent), although hexanol did not. Carnitine acyltransferase, while often associated with peroxisomal changes, can be activated by changes in mitochondria as well. In other phthalates, electron microscopy revealed an absence of structural evidence of peroxisome proliferation, even with increased carnitine acyltransferase activity. Study authors posited mitochondrial changes were responsible for the increased activity of hepatic carnitine acyltransferase in the presence of these phthalates (Gray et al. 1983).

A chemical's ability to inhibit intercellular communication *in vitro* has been correlated with its ability to promote tumors in mice (Klaunig et al. 1987; Ruch and Klaunig 1987; Ruch et al. 1987). The effect of eight straight and branched chain phthalate esters, including 5-100 μ M mono-n-hexyl phthalate, on intercellular communication was studied in male B6C3F1 mouse hepatocytes. After eight hours of exposure, straight chain monoesters, including mono-n-hexyl phthalate, had no effect on intercellular communication in mouse hepatocytes (Klaunig et al. 1988).

Nervous System

Lu et al. (2004) investigated the effects of eight dialkyl phthalates including di-n-hexyl phthalate, on the calcium signaling of acetylcholine receptors (AChR's) using human neuroblastoma SH-SY5Y cells. AChRs are the site of neurotransmissions in the central and peripheral nervous systems and play an important role in learning and memory, and modulation of blood catecholamine, heart rate, and blood pressure. AChRs serve as ion channels in neuron cells and are regulated by antagonizing and agonizing ligands. With varying potencies, all eight phthalates inhibited agonist-induced calcium signaling in the human nicotinic AChR. The compounds in order of strongest to weakest inhibition potency were: di-n-pentyl phthalate (DPP) > butyl benzyl phthalate (BBP) > di-n-butyl phthalate (DBP) > dicyclohexyl phthalate (DCHP) > di-n-hexyl phthalate (DnHP) > di-(2-ethyl hexyl) phthalate (DEHP) > di-n-propyl phthalate (DPrP) > diethyl phthalate (DEP). Dialkyl group carbon numbers of C4 or C5 were associated with the strongest inhibition; carbon numbers less than four and greater than five were less potent. At concentrations as low as 0.1 μ M, DPP, DBP, BBP, DCHP and DnHP significantly inhibited the calcium signaling of human nicotinic AChR. The IC_{50} (i.e., the concentration at which calcium signaling was inhibited by 50 percent) for DnHP was 0.56 μ M for human nicotinic AChR. A similar trend had been previously noted in bovine chromaffin cells, but IC_{50}

values in bovine nicotinic AChR were higher (31.6 μ M in DnHP). The significance of this type of inhibition of neurotransmission is not yet understood (Lu et al. 2004).

Endocrine System

Di-n-hexyl phthalate concentrations ranging from 10^{-3} M to 5×10^{-7} M did not show any evidence of estrogenic activity in the recombinant yeast screen (Harris et al. 1997). DnHP also did not induce proliferation of MCF-7 or ZR-7, two estrogen-responsive human breast cancer cell lines.

Using a battery of *in vitro* and *in vivo* assays, Zacharewski et al. (1998) investigated the potential estrogen receptor (ER)-mediated activity of 1-1000 μ M DnHP. DnHP weakly competed with estradiol for binding to the rat uterine ER in an *in vitro* competitive ligand-binding assay. Displacement of estradiol (E2) from the ER was less than 50 percent and therefore, a 50 percent inhibition concentration (IC_{50}) value could not be calculated. In another assay, 10 μ M DnHP, but not 0.1 or 1.0 μ M, significantly but weakly (16 percent) induced luciferase activity in transiently transfected MCF-7 cells when compared to the response induced by 10 nM E2. No estrogenic response was observed following exposure to 0.1-10 μ M DnHP in HeLa cells stably transfected with Gal4-HEG0 and 17m5-G-Luc. Finally, the recombinant *Saccharomyces cerevisiae* yeast strain PL3 was transformed with YEplO vectors containing the human estrogen receptor cDNA and exposed to 10 μ M DnHP. No estrogenic response was observed.

The estrogenic activity of DnHP was also assessed *in vivo* by monitoring two classical estrogenic responses, estrogen induction of uterine wet weight and the cornification of vaginal epithelial cells. Sprague-Dawley rats were dosed via gavage with 20, 200, or 2000 mg/kg bw of DnHP, or 1 mg/kg E2, for four days. Di-n-hexyl phthalate did not induce dose-dependent ER-mediated increases in uterine wet weight or vaginal epithelial cell cornification (Zacharewski et al. 1998). The absence of an *in vivo* estrogenic response to DnHP suggests that metabolic events inactivate the estrogenic activity of DnHP (Zacharewski et al. 1998).

Reproductive and Developmental Toxicity

Testicular atrophy induced by di-n-hexyl phthalate exposure has been well documented in the literature. *In vivo* and *in vitro* studies indicate that Sertoli cells are the primary site of damage caused by di-n-hexyl phthalate in the testes. The incubation of rat-derived Sertoli and germ cell cultures with 1, 10, or 100 μ M mono-n-hexyl phthalate, the immediate metabolite of DnHP, resulted in a dose-dependent detachment of germ cells from the Sertoli cell monolayer within the first 24 hours of exposure. The detached germ cells remained viable and were unchanged structurally, but changes in the morphology of Sertoli cells were noted (Gray and Beamand 1984). Similar results implicating Sertoli cells as the primary site of injury have been described with other phthalates (Gangolli 1982; Creasy et al. 1983; Granholm et al. 1992; Jones et al. 1993; Gray and Gangolli 1986).

In a study of the relative reproductive toxicity of eight phthalate esters to rats, dihexyl phthalate caused the second most severe testicular atrophy after diamyl phthalate (Foster et al. 1980). Four-week old rats received 2400 mg/kg bw/day dihexyl phthalate via gavage for four days. Following exposure, relative testis weight was 64.8 percent that of control ($p < 0.001$).

Histological analysis showed seminiferous tubule atrophy with most tubules showing few spermatogonia and Sertoli cells, but normal Leydig cell morphology. An accompanying increase in urinary zinc was noted, likely the result of a concomitant depression in gonadal zinc metabolism. Zinc level changes were not observed in rats given phthalate compounds *not* associated with testicular injury (Foster et al. 1980).

The National Toxicology Program (NTP) evaluated the reproductive toxicity of DnHP using the Fertility Assessment by Continuous Breeding protocol in Swiss CD-1 mice as part of a structure-activity evaluation of a variety of phthalates. Male and female mice (20/sex/dose) received DnHP at concentrations of 0.3, 0.6, and 1.2 percent in feed (approximately equivalent to 380, 800, and 1670 mg/kg/day, respectively) for seven days prior to and during a 98-day cohabitation. A concurrent control group of 40 pairs was run. The reproductive NOAEL was determined to be less than 380 mg/kg/day based on significant decreases in the mean number of litters per pair (n=343 vs. 489 in control), the number of live pups/litter (n=343 vs. 1229 in control), and the proportion of pups born alive. Of 17 pairs, 14 had litters, compared to 100 percent in the control group. At the middle and high doses, there were one and zero litters born, respectively. These effects occurred in the absence of an effect on postpartum dam body weights (NTP 1997).

Results of a follow up crossover mating experiment using control and high-dose mice indicated that the toxicity of DnHP to fertility was strongly but not exclusively a result of paternal exposure. The mating index (proportion of pairs showing successful copulation) was 90 percent in control pairs, 88 percent in control male x treated female pairs, and 56 percent in treated male x control female pairs. Treated female mice therefore, were sexually receptive; however, none became pregnant. Only 1 of 18 treated males sired a litter when crossed with a control female mouse. Effectively, both sexes were infertile at this level of DnHP exposure.

High-dose and control mice of the parental generation were necropsied following crossover mating. Body weights of DnHP-exposed F0 females were slightly less (6 percent) than controls, while adjusted weights of livers were increased by 32 percent and adjusted kidney weights and uterine weights were decreased by 6 percent and 31 percent, respectively. No treatment-related microscopic lesions were detected in the ovaries, uterus, or vagina. The high dose of DnHP in males was also associated with decreased body weight (10 percent less than control) and decreased absolute testis weight (70 percent less). Body-weight-adjusted liver weights were increased by 34 percent, and adjusted weights of kidney, epididymis, and seminal vesicles were reduced by 9, 23, and 18 percent, respectively. Epididymal sperm concentration and motility were reduced by 93 percent and 80 percent, respectively. The percent of abnormal sperm was not different from controls (NTP 1997).

Female CD-1 mice were dosed by gavage during gestation days 6–13 with 9900 mg/kg/day di-n-hexyl phthalate for the purpose of screening for teratogenicity. Maternal survival was good (98 percent), but no viable litters were produced from 34 confirmed matings (Hardin et al. 1987). No further information was available on this study, and no useful conclusions could be drawn from these results because the dose used was so high.

Genotoxicity

Di-n-hexyl phthalate tested negative in a reverse mutation assay using *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537. Bacteria were exposed to five concentrations of the test substance, up to 10 mg/plate in the presence or absence of S9 preparation. Dihexyl phthalate did not induce significant incidences of reverse mutation in the presence or absence of metabolic activation under conditions described here (Zeiger et al. 1985).

The American Chemistry Council (ACC) has reported that diisohexyl phthalate (which may contain up to 25 percent DnHP) was negative for mutagenicity in a mouse micronucleus test that was conducted by Exxon Biomedical Sciences in 1996 (CMA 1999).

No further data were identified on the genotoxicity of di-n-hexyl phthalate.

Carcinogenicity

No data on the carcinogenicity of di-n-hexyl phthalate were identified in a search of the literature.

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**Table 6: Summary of Toxicity Data for 1,2-Benzenedicarboxylic Acid, Dihexyl Ester
(CAS #84-75-3)**

Organ/ System	Model	Exposure Route	Dose	Dose Duration	Endpoint	Effect	Reference
Liver	Wistar rats	Dietary	1,824 mg/kg bw/day	3, 10, or 21 days	NOAEL <1824 mg/kg bw/day	<p><u>Starting at 3 d:</u> proliferation and dilation of smooth endoplasmic reticuli; shortening of the microvilli in bile canaliculi</p> <p><u>Starting at 10 d:</u> loss of glycogen; centrilobular fatty accumulation; centrilobular necrosis; lipid droplets; ↑ catalase activity in the large particular fraction; ↑ cyanide-insensitive palmitoyl-CoA oxidase activity (at 10 d only);</p> <p><u>Starting at 21 d:</u> ↑ liver wt; ↑ glucose-6-phosphatase activity.</p>	Mann et al. 1985
Liver, thyroid	Wistar rats	Dietary	10,000 ppm (~920 mg/kg/day)	14 days	NOAEL <920 mg/kg/day	Fat accumulation in liver, ↓ serum cholesterol, ↑ triiodothyronine; ↓ thyroxine	Howarth et al. 2001
Liver	Rat hepatocytes	In vitro	Monohexyl phthalate 0.2 mM	48 hours	NR	↑ carnitine acyltransferase activity; ↑ cyanide-insensitive palmitoyl-CoA oxidation	Gray et al. 1983

Liver	Male B6C3F1 mouse hepatocytes	In vitro	5-100 µM		NOEL = 100 µM	No effect on intercellular communication	Klaunig et al. 1988
Nervous System	Human neuroblastoma SH-SY5Y cells	In vitro	0.1-10 µM	100 sec's before agonist	IC ₅₀ = 0.56 µM	Suppression of calcium signaling at nicotinic acetylcholine receptors.	Lu et al. 2004
Endocrine	Recombinant yeast screen	In vitro	10 ⁻³ M - 5x10 ⁻⁷ M		NOEL = 10 ⁻³ M	Negative for estrogenic activity	Harris et al. 1997
Endocrine	Sprague-Dawley rat uterus cells Transiently transfected MCF-7 cells Stably transfected HeLa cells Transformed <i>S. cerevisiae</i> strain PL3		1-1000 µM 0.1-10 µM 0.1-10 µM 10µM			Weakly competed with E2 for uterine ER binding. Weakly (16%) induced luciferase activity at 10 µM No estrogenic response. No estrogenic response.	Zacharewski et al. 1998
Endocrine	Sprague-Dawley rats	Gavage	20, 200, or 2000 mg/kg bw	4 days	NOEL = 2000 mg/kg bw	No induction of dose-dependent, ER-mediated increases in uterine wet wt or vaginal epithelial cell cornification.	Zacharewski et al. 1998
Reproductive	Rat testicle cell	In vitro	1, 10, 100 µM mono-n-hexyl phthalate	24-48 hrs	NOAEL < 1.0 µM	Dose-dependent detachment of germ cells from the Sertoli cell monolayer; morphological changes to Sertoli cells.	Gray and Beamand 1984
Reproductive	Rats	Gavage	2400 mg/kg bw/day	4 days	NOAEL < 2400 mg/kg/day	↓ Relative testis wt. (seminiferous tubule atrophy; few spermatogonia and Sertoli cells, normal Leydig cell morphology); ↑ urinary zinc	Foster et al. 1980

Reproductive	Swiss CD-1 mice (male and female)	Dietary	380,800, 1670 mg/kg/day	7 days prior to and during a 98-day cohabitation followed by crossover mating with some control x high-dose animals	NOAEL _{reproductive} <380 mg/kg/day NOAEL _{systemic} <1670 mg/kg bw /day	↓ litters/pair, live pups/litter, proportion live births. <u>At 1670 mg/kg/day</u> (no other doses examined for systemic effects):: F: ↑ adjusted liver wt, ↓ adjusted kidney and uterine wts; M: ↓ body wt, ↑ adjusted liver wt, ↓ absolute testis wt, ↓ adjusted wt of kidneys epididymis, and seminal vesicle, ↓ epididymal sperm concentration and motility. Cross over mating: ↓ mating index with either treatment x control combination. All groups infertile.	NTP 1997
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1,2-BENZENEDICARBOXYLIC ACID, DIHEXYL ESTER, BRANCHED AND LINEAR (CAS #68515-50-4)

1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear (CAS #68515-50-4) is a mixture of $\leq 25\%$ di-n-hexyl phthalate (CAS #84-75-3; DnHP) and diisohexyl phthalates (CAS #'s 146-50-9 and 71850-09-4) (CERHR 2003). No toxicity data were identified for 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear.

Diisohexyl phthalate was tested for dermal irritation and sensitization among 104 people. No irritation was noted after a 24-hour occluded patch exposure of undiluted diisohexyl phthalate to human skin. There was also no evidence for dermal sensitization in the human repeated insult patch test (HRIPT) (Medeiros et al. 1999).

Data for di-n-hexyl phthalate, a component of 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear, are summarized elsewhere in the present review and the reader is referred to that summary.

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1,2-BENZENEDICARBOXYLIC ACID, DIHEPTYL ESTER, BRANCHED AND LINEAR (CAS #68515-44-6)

1,2-Benzenedicarboxylic acid, diheptyl ester branched and linear (CAS #68515-44-6) is an ortho-phthalate diester with side chains comprising primarily seven carbon atoms. Approximately 30 percent of the molecules in this substance have carbon backbones in the C4-C6 range, classifying it as a transitional phthalate (U.S. EPA 2001).

There were few toxicity or exposure data available for 1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear. Data on 1,2-benzenedicarboxylic acid, diheptyl ester (DnHP; CAS #3648-21-3) and 1,2-benzenedicarboxylic acid, diisooheptyl ester (DIHP; CAS #41451-28-9) are presented here where those for the branched and linear compound are absent. DIHP comprises primarily (80 percent) methyl-hexyl isomers, as well as some di-methyl pentyl isomers (McKee et al. 2006).

Exposure

No exposure data were identified for 1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear (diheptyl phthalate, branched and linear). DIHP (CAS #41451-28-9) is used primarily in flooring manufacture. In nine independent occupational hygiene surveys, DIHP was not detected (detection limits = 0.01 – 2.0 mg/m³). In two flooring manufacturing facilities, the mean levels in the air were 0.11-0.23 mg/m³. Assuming an inhalation rate of 10 m³/day and a 70 kg body weight, 100 percent absorption would equate to a daily average exposure of 16-32 µg/kg bw/day (McKee et al. 2006).

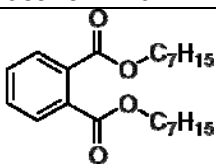
Consumer exposure to diisooheptyl phthalate would be through dermal contact with flooring itself, or from contaminated media. An unpublished survey of phthalates in environmental media reported 50 ng/m³ DIHP in dust, <6 ng/g dry weight in soil, and undetectable concentrations in outdoor air (LOD = 10 ng/m³), milk (LOD = 10 ng/m³), or vegetation samples (LOD = 100 ng/g) (reported in McKee et al. 2006). DIHP was detected in sole (2.89 ng/g lipid equivalent), crabs (1.89 ng/g), oysters (2.15 ng/g), and mussels (2.85 ng/g) collected in Vancouver, British Columbia (Mackintosh et al. 2004).

Di-n-heptyl phthalate was detected in 2 of 46 human adipose tissue samples analyzed for the Fiscal Year 1982 National Human Adipose Tissue Survey (Onstot et al. 1987).

Physicochemical Properties

The physicochemical properties of 1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear are listed below in Table 7.

Table 7: Physicochemical Properties of 1,2-Benzenedicarboxylic Acid, Diheptyl Ester, Branched and Linear

Identification	Information
Chemical Name	1,2-Benzenedicarboxylic acid, diheptyl ester, branched and linear
Synonyms	1,2-Benzenedicarboxylic acid, diheptyl ester; Branched and linear diheptyl phthalate; Phthalic acid, dialkyl(C7) ester; 1,2-Benzenedicarboxylic acid, diheptyl ester, branched and linear ; Palatinol 7P
CAS Number	68515-44-6
Structure	
Chemical Formula	C ₂₂ H ₃₄ O ₄
Molecular Weight	362.5
Physical State	Liquid
Melting Point	-45°C
Boiling Point	364°C @ 1013 hPa
Vapor Pressure	9.33x10 ⁻⁷ – 1.08x10 ⁻⁵ @25°C
Water Solubility	0.002 - 0.02 mg/L @25°C
Log K _{ow}	6.87-7.81
Source	U.S. EPA 2006

Toxicokinetics

The absorption, distribution, metabolism, and excretion of di(5-methylhexyl) phthalate (DMHP; CAS #41451-28-9) were studied in 6 week old male Wistar rats. Orally administered ¹⁴C-DMHP (250 mg/kg bw) was rapidly absorbed. After 24 hours, there was some activity in the kidney, liver, stomach, and intestine, but DMHP did not appear to remain in any organ or tissue. After seven days, 60 and 30 percent of the radioactivity was found excreted into the urine and feces, respectively. Biliary excretion amounted to about 15 percent of the dose after 4 days. Four major metabolites, all monoesters, were isolated in the urine: 5-hydroxy-5-methylhexyl phthalate, 6-hydroxy-5-methylhexyl phthalate, 5-carboxyhexyl phthalate, and 3-carboxypropyl phthalate. Unchanged DMHP and mono-5-methylhexyl phthalate (MMHP) were found along with a small amount of phthalic acid in the feces. MMHP and its glucuronide conjugate were detected in the bile. Data from previous experiments in this laboratory indicate that metabolites in the bile were excreted into the intestine and the glucuronides were hydrolyzed to MMHP (Sato et al. 1984).

Acute Toxicity

There were no data identified on the acute toxicity of 1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear. The oral LD₅₀ of the similar compound, 1,2-benzenedicarboxylic acid, di-C6-C8 branched alkyl esters, C7-rich was determined to be >10,000 mg/kg b.w. in rats. The dermal LD₅₀ of this compound in rabbits was >3160 mg/kg b.w. (ECB 2000).

Irritation and Sensitization

There were no data identified on the acute toxicity of 1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear. 1,2-Benzenedicarboxylic acid, di-C6-C8 branched alkyl esters, C7-rich was classified as slightly irritating to the skin and eyes of rabbits, and not irritating under the EC classification (ECB 2000). In a GLP guinea pig maximization test, 1,2-benzenedicarboxylic acid, di-C6-C8 branched alkyl esters, C7-rich was not sensitizing (ECB 2000).

1,2-Benzenedicarboxylic acid, di-C6-C8 branched alkyl esters, C7-rich (diisoheptyl phthalate) was tested for dermal irritation and sensitization among 104 people. No irritation was noted after a 24 hour occluded patch exposure of undiluted diisoheptyl phthalate to human skin. There was also no evidence for dermal sensitization in the human repeated insult patch test (HRIPT) using the modified Draize p ion potential (Medeiros et al. 1999).

Systemic Toxicity

Di-n-heptyl phthalate (CAS #3648-21-3) was administered via intragastric administration to F344 rats (5/sex/dose) at 0, 200, 1000 or 5000 mg/kg/day for 28 days. Reduction of body weight gain was observed in males and females in the 5000 mg/kg group. Males in all dose groups had significant increases in albumin and albumin/globulin ratio, and females in the top two groups showed increased albumin and total protein. Males receiving the high and middle dose of di-n-heptyl phthalate had increases in certain blood protein levels and Zn (high dose only); in females, only one protein level was elevated. Liver weights were higher in both sexes treated with 1000 and 5000 mg/kg/day; these males also presented with swelling and necrosis of hepatocytes. In high-dose males, kidney weights were higher and testicular weights lower when compared to controls. These males showed atrophy of the seminiferous tubules and loss of spermatogenesis. Two weeks after dosing had ended, testes changes remained, but some of the seminiferous tubules showed slight regenerative changes (Matsushima et al. 1992).

Endocrine effects

Using a battery of *in vitro* and *in vivo* assays, Zacharewski et al. (1998) investigated the potential estrogen receptor (ER)-mediated activity of 1-1000 µM diisoheptyl phthalate (99.6 percent purity). Diisoheptyl phthalate did not compete with estradiol for binding to the rat uterine estrogen receptor (ER) in an *in vitro* competitive ligand-binding assay at concentrations of 1-1000 µM. In addition, 0.1-10 µM diisoheptyl phthalate failed to induce luciferase activity in transiently transfected MCF-7 cells when compared to the response induced by E2. No estrogenic response was observed following exposure to 0.1-10 µM diisoheptyl phthalate in HeLa cells stably transfected with Gal4-HEG0 and 17m5-G-Luc. Finally, the recombinant *Saccharomyces cerevisiae* yeast strain PL3 was transformed with YEplO vectors containing the

human estrogen receptor cDNA and exposed to 10 μ M diisoheptyl phthalate. No estrogenic response was observed.

The estrogenic activity of diisoheptyl phthalate was also assessed *in vivo* by monitoring two classical estrogenic responses, estrogen induction of uterine wet weight and the cornification of vaginal epithelial cells. Sprague-Dawley rats were dosed via gavage with 20, 200, or 2000 mg/kg of diisoheptyl phthalate, or 1 mg/kg E2, for four days. Diisoheptyl phthalate did not induce dose-dependent ER-mediated increases in uterine wet weight or vaginal epithelial cell cornification, providing additional evidence that this compound cannot be classified as “estrogenic” (Zacharewski et al. 1998).

Reproductive and Developmental Toxicity

Rats were administered 2600 mg/kg bw/day di-n-heptyl phthalate by oral gavage for four days. No adverse effects on testes, including changes in relative weight were noted. As well, no changes in testicular or urinary zinc level were observed (Foster et al. 1980).

McKee et al. (2006) administered female Crl:CDBR rats 100, 300, or 750 mg/kg diisoheptyl phthalate (CAS #41451-28-9) by oral gavage on gestational days (GD) 6-20. At the high dose, there were significant reductions in uterine weight, and at 300 and 750 mg/kg, dam liver weights were significantly increased. The maternal NOAEL was 100 mg/kg based on increased liver weight. Observations at the high-dose level included increased resorptions, post-implantation loss, reduced fetal weight, decreased viable fetuses per dam, and changes in fetal sex distribution. In addition, the incidence of litters with external, visceral, or skeletal malformations was significant at the high-dose level. Therefore, the developmental NOAEL was 300 mg/kg/day (McKee et al. 2006).

Diisoheptyl phthalate was administered to rats in the diet at 0, 1000, 4500, or 8000 ppm in a two-generation reproductive toxicity study. Food was offered continuously from 70 days pre-mating, throughout mating, gestation, and lactation. In offspring (i.e., the F1 generation) of the high-dose parental generation, anogenital distance was reduced, time to balanopreputial separation was increased, there was a significant increase in thoracic nipples and testicular abnormalities, and weights of testes and accessory reproductive organs were significantly reduced. Testicular sperm counts and daily sperm production were significantly reduced at all dose levels; however, only at the high dose were there concurrent changes (like reproductive organ weights and epididymal sperm count changes) supporting a treatment-related effect. Fertility and mating indices were significantly reduced in F1 males and females of the high dose group. Their offspring (the F2 generation) showed significantly reduced anogenital distances and reduced weight gain during lactation in both the 4500 and 8000 ppm groups, and reduced relative spleen weight at the high dose. The NOEL for reproductive and developmental toxicity therefore, was based on effects on F2 rats with parents receiving 4500 ppm diisoheptyl phthalate; the dose was approximately 64 mg/kg/day during gestation, and 144 mg/kg/day during the first two weeks of lactation (McKee et al. 2006).

In ICR mice treated on GD 7-11 with diisoheptyl phthalate doses of 0.94-11.3 mL/kg (~940-11,300 mg/kg), embryoletality was observed at the highest dose level and fetal abnormalities

were seen at the mid- and high-dose levels. A NOEL of 9407 mg/kg was determined (HSDB 2010). No further details were available for this study.

Pregnant ICR:JCL mice were treated with single oral doses of di-n-heptyl phthalate on GD 7, 8, 9, 10, or 11. Approximate dose levels were 940, 1880, or 3750 mg/kg on day 7; 1500, 2500, or 7500 mg/kg on day 8 or 9; and 7500 or 11,300 mg/kg on day 10 or 11. Embryo-fetal toxicity was highest on days 7 and 8, with 100 percent of the fetuses being resorbed on day 8 when treated with 7500 mg/kg of diheptyl phthalate. On the other hand, toxicity was low on GDs 10 and 11 even at the high dose. The frequency of gross fetal abnormalities was increased on days 8 and 9, with 66.7 percent (middle dose) or 73.9 percent (high dose) of the fetuses abnormal. On day 8, the most common gross abnormality was exencephalia; on day 9, it was open eyelid, cleft palate, and oligodactylia on day 9; and on GDs 10 and 11, tail anomaly, oligodactylia, and hematoma. Skeletal effects included deformities of the vertebrae, fused ribs, abnormal or incomplete skull bones, and incomplete or missing leg bones. Fused ribs occurred in 100 percent of the fetuses exposed to 2500 mg/kg on GD 8 (Nakashime et al. 1977).

Genotoxicity

No genotoxicity data were identified for diheptyl phthalate, branched and linear.

Sato et al. (1994) evaluated mutagenic properties of di-n-heptyl phthalate using a reverse mutation (Ames) assay. In the reverse mutation assay, *Salmonella typhimurium* tester strain TA98 was exposed to di-n-heptyl phthalate concentrations of 0.25-500 µmol/plate in the presence and absence of rat liver S9 mix. Di-n-heptyl phthalate was negative for mutagenicity in both the presence and absence of metabolic activation (Sato et al. 1994).

Carcinogenicity

There were no data identified on the carcinogenicity of diheptyl phthalate, branched and linear.

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Table 8: Summary of Toxicity Data for 1,2-Benzenedicarboxylic Acid, Diheptyl Ester, Branched and Linear (CAS #68515-44-6)

Organ/ System	Model	Exposure Route	Dose	Dose Duration	Endpoint	Effect	Reference
Systemic	F-344 rats	Gavage	Di-n-heptyl phthalate: 0, 200, 1000 or 5000 mg/kg/day	28 days	NOAEL <200 mg/kg/day	200 mg/kg/day: ↑ albumin and albumin/globulin ratio (M) 1000 and 5000 mg/kg/day: ↓ body wt gain (M and F); ↑ liver wt (M and F); ↑ albumin and total protein (F); ↑ certain blood protein levels and Zn (M) 5000 mg/kg/day: ↑ kidney wt (M); ↓ testicular wt including atrophy of the seminiferous tubules and loss of spermatogenesis.	Matsushima et al. 1992
Endocrine	Sprague-Dawley rat uterus cells Transiently transfected MCF-7 cells Stably transfected HeLa cells Transformed <i>S. cerevisiae</i> strain PL3;	In vitro	Diisoheptyl phthalate: 1-1000 µM 0.1-10 µM 0.1-10 µM 10µM			Did not compete with E2 for uterine ER binding. Did not induce luciferase activity No estrogenic response No estrogenic response	Zacharewski et al. 1998
Endocrine	Sprague-Dawley rats	Gavage	Diisoheptyl phthalate: 20,	4 days	NOAEL = 2000 mg/kg/day (highest	No induction of ER- mediated increases in	Zacharewski et al. 1998

			200, or 2000 mg/kg bw		dose)	uterine wet wt or vaginal epithelial cell cornification.	
Reproductive	Rats	Gavage	<u>Di-n-heptyl phthalate</u> : 2600 mg/kg bw/day	4 days	NOAEL = 2600 mg/kg/day (only dose)	No adverse effects on testes or urinary zinc level were observed.	Foster et al. 1980
Reproductive/ Developmental	Crl:CDBR rats	Gavage	<u>Diisoheptyl phthalate</u> 100, 300, or 750 mg/kg	GDs 6-20	NOAEL _{maternal} = 100 mg/kg/day NOAEL _{developmental} = NOAEL _{reproductive} = 300 mg/kg/day	<u>300 mg/kg/day</u> : ↑ dam liver wts <u>750 mg/kg/day</u> : ↑ dam liver wts; ↓ uterine wt; ↑ resorptions, post-implantation loss, reduced fetal wt, decreased viable fetuses per dam, and changes in fetal sex distribution; ↑ litters with external, visceral, or skeletal malformations.	McKee et al. 2006
Reproductive/ Developmental	Crl:CD rats	Dietary	0, 1000, 4500, or 8000 ppm <u>diisoheptyl phthalate</u>	F0: 70 days premating, throughout mating, gestation, and lactation	NOAEL _{developmental} = NOAEL _{reproductive} = 64 - 144 mg/kg/day	↓ wt gain during gestation and lactation in offspring of 4500 ppm parents <u>Offspring of 8000 ppm parents</u> : ↓ anogenital distance (F1), ↑ time to balanopreputial separation (F1), ↑ in thoracic nipples and testicular abnormalities (F1), ↓ testis and accessory reproductive organs wts (F1); ↓ testicular sperm counts and daily sperm production with evidence of treatment-related effect; ↓ fertility and mating indices (F1 males and	McKee et al. 2006

						females); ↓ anogenital distances (F2); ↓ wt gain during lactation (F2); ↓ relative spleen wt (F2).	
Developmental	ICR mice	(not available)	<u>Diisoheptyl phthalate</u> 940-11,300 mg/kg	GD 7-11	NOEL = 9407 mg/kg	Embryo lethality, fetal abnormalities	HSDB 2010
Developmental	ICR:JCL mice	Oral (unspecified)	<u>Di-n-heptyl phthalate</u> : 940, 1880, 3750 mg/kg; 1500, 2500, 7500 mg/kg; 7500, 11,300 mg/kg	GD 7 GD 8 or 9 GD 10 or 11	NOAEL <940 mg/kg bw given on GD 7	Embryo-fetal toxicity was highest w dosing on GDs 7 and 8, and lowest on GDs 10 and 11, even at the high dose. Frequency of gross fetal abnormalities, GD 8/9 dosing = 66.7% (middle dose) and 73.9% (high dose).	Nakashime et al. 1977

1,2-BENZENEDICARBOXYLIC ACID, DI-C6-8-BRANCHED ALKYL ESTERS, C7-RICH (CAS 71888-89-6)

1,2-Benzenedicarboxylic acid, di-C6-8 branched alkyl esters, C7-rich (CAS #71888-89-6) is primarily phthalate esters with C7 branched chains. Approximately 15 percent of the molecules in this substance have carbon backbones in the C4-C6 range, classifying it as a transitional phthalate (U.S. EPA 2001). Di-C6-8 branched alkyl phthalate esters, C7 rich is a component of 711P and 79P, two high molecular weight phthalate ester mixtures.

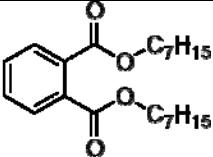
There were few toxicity or exposure data available for 1,2-benzenedicarboxylic acid, di-C6-8 branched alkyl esters, C7-rich (also called di-C6-8 branched alkyl phthalate esters, C7 rich). In the absence of data on this compound, data on 1,2-benzenedicarboxylic acid, diisooheptyl ester (CAS #41451-28-9) can be used to describe toxicity; those studies are summarized in the previous section on 1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear.

Exposure

The occupational exposure limit (OEL) established by Exxon Chemicals for di-C6-8 branched alkyl phthalate esters, C7-rich is 5 mg/m³ (ECB 2000). The basis for this OEL was not identified.

Physicochemical Properties

The physicochemical properties of di-C6-8 branched alkyl phthalate esters, C7-rich are listed below in Table 9.

Table 9: Physicochemical Properties of 1,2-Benzenedicarboxylic Acid, di-C6-8 Branched Alkyl Esters, C7-Rich	
Identification	Information
Chemical Name	1,2-Benzenedicarboxylic acid, di-C6-8 branched alkyl esters, C7-rich
Synonyms	Di-C7 branched alkyl esters; Diisooheptyl phthalate; C7-Rich di-C6-8-branched alkyl phthalates; Jayflex 77
CAS Number	71888-89-6
Structure	 (one of several possible structures)
Chemical Formula	C ₂₂ H ₃₄ O ₄ (based on C7/C7)
Molecular Weight	362.5
Physical State	Liquid
Melting Point	-40°C

Boiling Point	>300°C @ 0.01 hPa
Vapor Pressure	< 0.01 hPa @20°C
Water Solubility	< 0.1 vol. % @ 20°C
Log K _{ow}	~ 7
Flashpoint	>190°C
Source	ECB 2000

Toxicokinetics

No data on the toxicokinetics of di-C6-8 branched alkyl phthalate esters, C7-rich were identified in a search of the literature. The toxicokinetics of the similar compound, diisooheptyl phthalate were described in the previous section on 1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear.

Acute Toxicity

The oral LD₅₀ of 1,2-benzenedicarboxylic acid, di-C6-C8 branched alkyl esters, C7-rich in rats was determined to be >10,000 mg/kg b.w. The dermal LD₅₀ in rabbits was >3160 mg/kg b.w. (ECB 2000).

Irritation and Sensitization

1,2-Benzenedicarboxylic acid, di-C6-C8 branched alkyl esters, C7-rich was classified as slightly irritating to the skin and eyes of rabbits, and not irritating under the EC classification (ECB 2000). In a GLP guinea pig maximization test, 1,2-benzenedicarboxylic acid, di-C6-C8 branched alkyl esters, C7-rich was not sensitizing (ECB 2000).

1,2-Benzenedicarboxylic acid, di-C6-C8 branched alkyl esters, C7-rich (diisooheptyl phthalate) was tested for dermal irritation and sensitization among 104 people. No irritation was noted after a 24-hour occluded patch exposure of undiluted diisooheptyl phthalate to human skin. There was also no evidence for dermal sensitization in the human repeated insult patch test (HRIPT) using the modified Draize patch test (Medeiros et al. 1999).

Systemic Toxicity

The hepatotoxicity of di-C6-8 branched alkyl phthalate esters, C7-rich (purity >98%) was evaluated along with five other phthalate diester compounds or mixtures (Smith et al. 2000). Male Fisher F344 rats (5/dose) were fed 1000 or 12,000 mg/kg bw phthalate diester and male B63F1 mice (5/dose) were fed 500 or 6000 mg/kg bw for two or four weeks. Biochemical indicators of hepatotoxicity were evaluated in both species: relative liver weight, peroxisomal beta oxidation (PBOX) level, gap junctional intercellular communication (GJIC), and DNA synthesis activity. PBOX activity was measured spectrophotometrically as the cyanide-insensitive reduction of NAD⁺ using palmitoyl-CoA as a substrate, GJIC was measured as the

distance of *in situ* dye transfer through adjacent hepatocytes and DNA synthesis activity was the fraction of hepatocytes labeled with bromodeoxyuridine. The high dose of di-C6-8 branched alkyl phthalate esters, C7-rich produced a statistically significant ($p > 0.05$) increase in relative liver weights in male rats after both two- and four-week exposures, while the low dose produced an increase at two, but not four weeks. Relative liver weights were unaffected in mice at all time and dose combinations. Both species exposed to the high dose of di-C6-8 branched alkyl phthalate esters, C7-rich had elevated PBOX after 2 and 4 weeks. No PBOX effect was observed at the low doses in either species. GJIC was unchanged for both species under all conditions. Low- and high-dose rats and high-dose mice at both time points had elevated periportal DNA synthesis activity. Low-dose mice showed this effect after two weeks, but not four (Smith et al. 2000).

The systemic toxicity of a structurally similar compound, diisooheptyl phthalate, were described in the previous section on 1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear.

Reproductive and Developmental Toxicity

No studies on the reproductive and developmental toxicity of di-C6-8 branched alkyl phthalate esters, C7-rich were identified in a search of the relevant literature.

Genetic Toxicity

The *in vitro* mammalian cytogenetic test under OECD Guideline 473 was employed to evaluate the genotoxicity of di-C6-8 branched alkyl phthalate esters, C7-rich. Chinese hamster ovary cells exposed to 12.5-4990 $\mu\text{g/mL}$ of the test substance in the presence and absence of metabolic activation showed no signs of mutagenicity (ECB 2000).

Carcinogenicity

No studies on the carcinogenicity of di-C6-8 branched alkyl phthalate esters, C7-rich were identified in a search of the relevant literature.

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**Table 10: Summary of Toxicity Data for 1,2-Benzenedicarboxylic Acid, Di-C6-8-Branched Alkyl Esters, C7-Rich
(CAS #71888-89-6)**

Organ	Model	Exposure Route	Dose	Dose Duration	Endpoint	Effect	Reference
Liver	Fisher F344 rats	Dietary	1000 or 12,000 mg/kg bw	2 or 4 weeks	NOAEL <1000 mg/kg bw	<u>1000 mg/kg</u> : ↑ relative liver wts after 2 weeks only; ↑ periportal DNA synthesis activity after 2 and 4 weeks; <u>12,000 mg/kg</u> : ↑ relative liver wts, ↑ PBOX, and ↑ periportal DNA synthesis activity after 2 and 4 weeks	Smith et al. 2000
Liver	B63F1 mice	Dietary	500 or 6000 mg/kg bw	2 or 4 weeks	NOAEL <500 mg/kg bw	<u>500 mg/kg</u> : ↑ periportal DNA synthesis activity after 2 weeks only; <u>6000 mg/kg</u> : ↑ PBOX and ↑ periportal DNA synthesis activity after 2 and 4 weeks	Smith et al. 2000

1,2-BENZENEDICARBOXYLIC ACID, HEPTYL UNDECYL ESTER, BRANCHED AND LINEAR (CAS #111381-90-9)

1,2-Benzenedicarboxylic acid, heptyl undecyl ester branched and linear (CAS #111381-90-9), also called branched and linear heptyl undecyl phthalate, is an *ortho*-phthalate diester with side chains comprising a mixture of primarily 7- and 11-carbon atoms. Approximately 15 percent of the molecules in this substance have carbon backbones in the C4–C6 range, classifying it as a transitional phthalate (U.S. EPA 2001). Branched and linear heptyl undecyl phthalate is only sold commercially as a component of phthalate ester mixtures like 711P, of which it comprises 1/6th (U.S. EPA 2001).

There were no toxicity, exposure, or use data identified for branched and linear heptyl undecyl phthalate.

References

United States Environmental Protection Agency (U.S. EPA). 2001. High Production Volume (HPV) Chemical Challenge Program. Test plan for the phthalate esters category. Submitted to the EPA by the Phthalate Esters Panel HPV Testing Group of the American Chemistry Council. <http://www.epa.gov/hpv/pubs/summaries/benzene/c13467tp.pdf>

1,2-BENZENEDICARBOXYLIC ACID, DINONYL ESTER (CAS #84-76-4)

1,2-Benzenedicarboxylic acid, dinonyl ester, generically referred to as dinonyl phthalate (DNP), is a linear ortho-dialkyl phthalate (*o*-DAP) with 9-carbon backbone. In a brief search of several chemical manufacturers of DNP, the purity of the commercial product is typically about 98 percent. DNP is used primarily as a plasticizer for polyvinyl chloride (PVC) to impart flexibility. It is considered a low efficiency plasticizer, because more DNP is required per polymer to produce the same hardness compared with a general plasticizer like diisooctyl phthalate (Whalen 1994). Specific applications employing a DNP plasticizer include vinyl in automotive interiors and insulation in electrical wire/cables (BASF 2002). DNP has been found in PVC toys and baby soothers (Sugita et al. 2001; CPSC 1998).

The U.S. EPA's Inventory Update Reporting program reported that 10,000–500,000 pounds of DNP were manufactured or imported in this country in 1993 (U.S. EPA 1994). Therefore, DNP is not considered a high production volume (HPV) compound by the U.S. EPA.

Exposure

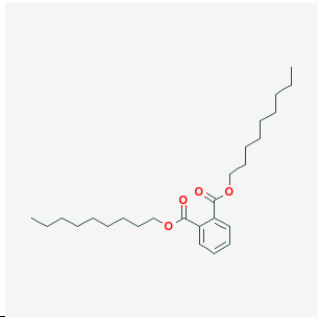
Occupational exposure to DNP may occur through inhalation of aerosols and dermal contact with this compound at workplaces where DNP is used in chromatography or as a plasticizer for vinyl resins (HSDB 2010).

The UK's Food Safety Directorate (now the Food Standards Agency) carried out a survey of the levels of total and individual phthalates in samples of composite fatty foods from a total diet study. The survey was carried out using stored samples of food, including carcass meat, meat products, offals, poultry, eggs, fish, fats, oils, milk, and milk products that had been collected in 1993. DNP was not detected (limit of detection = 0.001 mg/kg) in any of the samples analyzed (MAFF 1996). In a year 2000 survey of toys from 17 different countries, DNP was detected (but not quantified) in 2 of 72 samples, 64 of which were made of PVC (Stringer et al. 2000).

Physicochemical Properties

The physicochemical properties of 1,2,-benzenedicarboxylic acid, dinonyl ester are summarized below in Table 11.

Table 11: Physicochemical Properties of 1,2,-Benzenedicarboxylic Acid, Dinonyl Ester	
Identification	Information
Chemical Name	1,2-Benzenedicarboxylic acid, dinonyl ester
Synonyms and Trade Names	1,2-Benzenedicarboxylic acid, 1,2-dinonyl ester; Dinonyl phthalate (DNP); Phthalic acid, dinonyl ester; Ditrimethylhexyl phthalate; Di-n-nonylphthalate (DnNP); Dinonyl 1,2-benzenedicarboxylate; Bisoflex

	91; Bisoflex D5NP; Bisolflex 91; Unimoll DN; Palatinol 9P; Jayflex L9P Plasticizer
CAS Number	84-76-4
Basic Structure	
Chemical Formula	C ₂₆ H ₄₂ O ₄
Molecular Weight	418.6
Physical State	Liquid
Color	Colorless
Melting Point	<25°C
Boiling Point	413°C
Vapor Pressure	0.133 kPa (205°C) (NICNAS 2007)
Water Solubility	1.74 x 10 ⁻⁵ mg/L @ 25°C*
Log K _{ow}	>2.12 (NICNAS 2007)
Flashpoint	215°C
Sources: ChemIDPlus 2010; HSDB 2010	

Toxicokinetics

No data on the toxicokinetics of DNP were identified in a search of the literature. Toxicokinetic properties of DNP are not expected to differ significantly from those of di-n-octyl phthalate (DnOP). A review of the oral toxicokinetics of DnOP can be found in the CPSC's review of this compound, dated March 8, 2010 (CPSC 2010). In general, the metabolism of diester phthalates occurs first by phase I biotransformation to a monoester followed by phase II biotransformation of the phthalate monoester to a glucuronide conjugate (Silva et al. 2003). DNP is expected to be metabolized to mono-nonyl phthalate (MNP) and n-nonanol via hydrolysis of a single ester link; a minor amount of phthalic acid is expected via hydrolysis of both ester linkages (ATSDR 1997; OME 2005). N-nonanol is further oxidized to a fatty acid and metabolized by the fatty acid oxidation pathway (CERHR 2003). No data were located on the specific identity of the glucuronidated metabolites, or their distribution.

Acute Toxicity

DNP demonstrates a low order of toxicity following acute exposure via oral and intraperitoneal (i.p.) routes. An oral LD₅₀ value of >20 g/kg body weight (bw) was derived in both mice and rats following single doses (Brown et al. 1970). Visible symptoms were limited to persistently wet fur. In guinea pigs, an oral LD₅₀ value of 21.5 g/kg bw was established for DNP (Lewis

2004). In an unpublished study, Eastman Kodak Co. determined oral and i.p. LD₅₀ values for DNP of >26 g/kg bw for both rats and mice (Kodak 1984).

Male ICR mice received single i.p. doses of pure dinonyl phthalate and were observed for seven days. No mortality or histological evidence of peritoneal injury was observed; the LD₅₀ was determined to be greater than 100 g/kg bw (Lawrence et al. 1973).

Male ICR mice (10 per group) receiving intradermal and ophthalmic exposure to undiluted DNP experienced no grossly observable irritation by either route (Lawrence et al. 1973). Similarly, undiluted DNP did not cause irritation to guinea pig skin (Bingham et al. 2001) or rabbit eyes (Lawrence et al. 1973). In three rats, inhalation of 5500 ppm dinonyl phthalate heated to 200°C for 1.5 hours caused nasal irritation (Bingham et al. 2001). No further details of the study were available.

Irritation and Sensitization

DNP is not expected to cause significant sensitization to the skin because it has been used as a solvent to test sensitization of other chemicals and is thus assumed to be unreactive (Stevens 1967). Skin sensitization by C7-9 and C9-11 phthalates was evaluated in guinea pigs via topical administration and intradermal injection. None of the specific phthalates tested induced a sensitization reaction (Brown et al. 1970).

Skin irritation by C7-9 and C9-11 phthalates was evaluated in a covered assay using New Zealand white rabbits and in an uncovered assay using New Zealand white rabbits and albino guinea pigs. In rabbits, no irritation was observed in either covered or uncovered tests. In guinea pigs, the skin became coarse, slightly thickened and some sloughing of surface layers was noted (Brown et al. 1970). DNP was classified as a slight skin irritant in an unpublished study performed by the Eastman Kodak Co. It was noted that there was no dermal absorption of DNP at 10 cc/kg. No further details from this study were available, including identification of the test species (Kodak 1984). A guinea pig test also indicated that DNP is slightly irritating to the skin, but not sensitizing (DuPont 1947).

Systemic Toxicity

A three-month exposure to 2 mg/kg b.w. dinonyl phthalate did not decrease body weight gain, change hematological properties, or alter liver and kidney functioning in cats (Scheftel 1994). No further details of this study were available. The Hazardous Substances Database (HSDB 2010) summarized a study by Timofievskaya et al. (1973) where DNP administered orally, topically, or via inhalation to mice in subacute and chronic experiments produced demyelination, paralysis, disturbances of central and peripheral nervous systems and cachexia. No other details were available on this study.

Rats exposed to saturated vapors of DNP at 28°C for 6 hours per day for 12 days showed “no effect” (Patty 1963, cited in HSDB 2010). No more detailed information was available.

Lagente et al. (1979) measured the effect of phthalate ester exposure on lecithin/cholesterol acyltransferase activity in human cells *in vitro*. Dinonyl phthalate concentrations ranging from

1-25 μM reduced enzyme activity. At 5 μM , inhibition was about 40 percent. Enzyme activity decreased in a dose-dependent manner and then leveled off. Further details were not included. Comparing results across phthalates, there appeared to be a trend where enzyme inhibition decreased with increasing phthalate molecular weight.

A chemical's ability to inhibit intercellular communication *in vitro* has been correlated with its ability to promote tumors in mice (Klaunig et al. 1987; Ruch and Klaunig 1987; Ruch et al. 1987). The effect of eight straight and branched chain phthalate esters, including 5-100 μM mono-n-nonyl phthalate, on intercellular communication was studied in male B6C3F1 mouse hepatocytes. After eight hours of exposure, straight chain monoesters, including mono-n-nonyl phthalate, had no effect on intercellular communication in the absence of cytotoxicity (Klaunig et al. 1988).

Endocrine System

In a study of the human mammary carcinoma cell line (MCF-7), dinonyl phthalate, along with six other phthalate compounds (dibutyl phthalate (DBP), benzyl butyl phthalate (BBP), diallyl phthalate (DAP), di-n-octyl phthalate (DnOP), diisodecyl phthalate (DIDP), and ditridecyl phthalate (DTP)) were evaluated for cell proliferation potency/efficiency. Dinonyl phthalate's proliferative effect was 35 percent that of 17 β -estradiol's, and was considered insignificant. In this assay, only BBP and DBP showed significant relative proliferative effect. None of the phthalates demonstrated significant relative proliferative potency compared to estradiol (Kim and Ryu 2006).

The competitive inhibition of the same six phthalate compounds versus estradiol was also evaluated in this study. DNP (100 μM), along with BBP and DOP showed weak relative binding affinity (RBA) for the human estrogen receptor (0.02 percent) compared to estradiol (RBA: 100 percent), while the RBA of the other phthalates was insignificant (Kim and Ryu 2006). The significance of these results for DNP is not obvious, as corresponding *in vivo* endpoints were not evaluated. However, results of an *in vivo* uterotrophic assay carried out on four other phthalates (BBP, DBP, DAP, and DTP) bring into question the relevance of the *in vitro* competitive inhibition results. Doses of estradiol (0.3, 3, or 30 $\mu\text{g/kg}$), or phthalate (20, 200, or 2000 mg/kg b.w.) were administered to Sprague-Dawley rats subcutaneously. Estradiol significantly increased uterine wet weights at each dose level, while none of the four phthalates induced an increase in uterine wet weight at any given dose. The increase in relative binding affinity and proliferative potency measured *in vitro*, therefore, may not be relevant to the action of these compounds in phthalate-exposed humans (Kim and Ryu 2006).

Neurological System

Dinonyl phthalate was found to be the active compound in *Rosa laevigata*, a botanical known to protect against H_2O_2 -induced oxidative stress (Choi et al. 2006). *In vitro*, the extract, as well as DNP itself (0.05-0.2 M) increased cell viability in the presence of H_2O_2 in PC12 cells. In the *in vivo* portion of this study, ICR mice were fed 5, 10, or 20 mg/kg/day DNP during a 28-day study. On day 21, amyloid beta peptide ($\text{A}\beta$), an inducer of cellular oxidative stress that has been associated with neurodegenerative disorders like Alzheimer's disease, was administered via intracerebralventricular injection. Mice were subsequently subjected to standard memory and learning tests, including the Y-maze test and the passive avoidance test. The $\text{A}\beta$ -injected mice

not receiving DNP exhibited significantly impaired spatial working memory in the Y-maze test. In comparison, mice receiving the high dose of DNP had significantly better spatial memory as measured by spontaneous alternation behavior in the Y-maze test. The number of total arm entries in the Y-maze test was unaffected by A β and DNP exposure. In the passive avoidance test, treatment with 10 or 20 mg/kg/day DNP attenuated the memory loss induced by A β (Choi et al. 2006). The biochemical significance of this is not understood.

Reproductive and Developmental Effects

No studies on the reproductive or developmental toxicity of dinonyl phthalate were identified in a review of the relevant literature.

Genotoxicity

Sato et al. (1994) evaluated mutagenic properties of dinonyl phthalate using a reverse mutation (Ames) assay and the SOS Chromotest. In the reverse mutation assay, *Salmonella typhimurium* tester strain TA98 was exposed to DNP concentrations of 0.25-500 μ mol/plate in the presence and absence of rat liver S9 mix. DNP was negative for mutagenicity in both the presence and absence of metabolic activation. DNP also did not enhance the mutagenicity of known genotoxins Trp-P-1 and Trp P-2 to *Escherichia coli* strain PQ37 cells in the SOS Chromotest (Sato et al. 1994).

No further genotoxicity data were identified in a review of the relevant literature on DNP.

Carcinogenicity

No studies on the carcinogenicity of dinonyl phthalate were identified in a search of the relevant literature.

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**Table 12: Summary of Toxicity Data for 1,2-Benzenedicarboxylic Acid, Dinonyl Ester
(CAS #84-76-4)**

Organ/ System	Model	Exposure Route	Dose	Dose Duration	Endpoint	Effect	Reference
Liver	Male B6C3F1 mouse hepatocytes	In vitro	5-100 μ M	8-hours		No effect on intercellular communication in the absence of cytotoxicity.	Klaunig et al. 1988
Endocrine	MCF-7	In vitro	100 μ M	Unknown	NOEL = 100 μ M	Insignificant proliferative effect relative to estradiol	Kim and Ryu 2006
Neurological	PC12 cells/ ICR mice	In vitro/ Dietary	0.05 – 0.2 M/ 5, 10, 20 mg/kg/day with or without amyloid beta peptide (A β)	48-hrs/ 28-days	(statistical significance of in vitro effect not given)/ NOEL = 5 mg/kg/day	At 10 or 20 mg/kg/day DNP attenuated the memory-loss induced by A β . At 20 mg/kg/day, mice had significantly better spatial memory compared to A β group.	Choi et al. 2006

1,2-BENZENEDICARBOXYLIC ACID, DINONYL ESTER, BRANCHED AND LINEAR (CAS #68515-45-7)

There are few toxicity and use data available for 1,2-benzenedicarboxylic acid, dinonyl ester, branched and linear (CAS #68515-45-7), also called dinonyl phthalate, branched and linear. Some toxicological endpoints were described using data on the predominantly linear phthalate plasticizer 711P, a commercial technical mixture derived from C7, C9 and C11 alcohols (BASF 2001). 711P is an equal-parts mixture of six phthalate esters consisting of C7, C9, and C11 ester side chains with about two-thirds linear and one-third branched (U.S. EPA 2001; Smith et al. 2000). These are represented as the following CAS numbers: 68515-45-7 (di C9); 68515-44-6 (di C7); 3648-20-2 (di C11); 111381-89-6 (C7, C9); 111381-90-9 (C7, C11); and 111381-91-0 (C9, C11). Products comprising a mixture of those six phthalate esters include Ferro's Santicizer® 711, BASF's Palatinol 711P, and Strip Aid, made by Dynatex International.

It should be noted that data for diisononyl phthalate (CAS #28553-12-0) were not considered in this review because that compound has been evaluated previously by the CPSC.

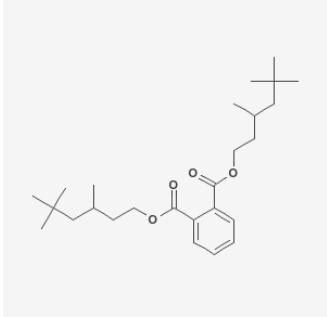
Exposure

No specific data on human exposure to dinonyl phthalate, branched and linear were identified in a search of the literature. Occupational exposure may occur through inhalation and dermal contact with this compound at workplaces where dinonyl phthalate, branched and linear is produced or used.

Physicochemical Properties

Some physical and chemical properties of dinonyl phthalate, branched and linear are summarized below in Table 13.

Table 13: Physicochemical Properties of Dinonyl Phthalate, Branched and Linear	
Identification	Information
Chemical Name	Dinonyl phthalate, branched and linear
Synonyms	1,2-Benzenedicarboxylic acid, dinonyl ester, branched and linear; 1,2-Benzenedicarboxylic acid, dinonyl ester; Branched and linear dinonyl phthalate; Phthalic acid, dialkyl(C9) ester
CAS Number	68515-45-7

Structure (one component shown)	
Chemical Formula	C ₂₆ H ₄₂ O ₄
Molecular Weight	420.63 (ChemIDPlus 2010)
Physical State	Liquid
Melting Point	-48°C
Boiling Point	454°C
Vapor Pressure	6.81 x 10 ⁻⁸ hPa
Water Solubility	0.00031 mg/L
Log K _{ow}	8.6
Flashpoint	218 (datum for Palatinol 79P; BASF 1996)
Source	U.S. EPA 2006 (unless otherwise noted)

Toxicokinetics

No data on the toxicokinetics of dinonyl phthalate, branched and linear were identified in a search of the literature.

Acute Toxicity

No data on the acute toxicity of dinonyl phthalate, branched and linear were identified in a search of the literature.

Irritation and Sensitization

No data on the irritation or sensitization properties of dinonyl phthalate, branched and linear were identified in a search of the literature.

Systemic Toxicity

No systemic toxicity data were identified for dinonyl phthalate, branched and linear in a search of the literature. The phthalate mixture Santicizer® 711P, which contains dinonyl phthalate, branched and linear, was evaluated in rats with respect to peroxisome proliferation. Barber et al. (1987) assessed the peroxisome induction of seven phthalate esters, including 711P. Several biomarkers of peroxisome proliferation were evaluated: relative liver weight, serum levels of triglyceride and cholesterol, and liver microsomal cyanide insensitive palmitoyl CoA (PCoA) oxidation, lauric acid 11-hydroxylase, and lauric acid 12-hydroxylase. Fischer 344 rats (5/sex/dose) were fed 2.5 percent, 1.2 percent, or 0.3 percent 711P in the diet for 21 days and then sacrificed. Following sacrifice, livers were weighed and samples were either fixed for

microscopic analysis or homogenized for enzyme analysis. The high dose of 711P was associated with a “moderate increase” in peroxisome content based on microscopic analysis of the periportal zone of the liver of two males. The increase in peroxisome content in female rats was “slight.” Changes in relative liver weight and PCoA oxidation, thought to be the most sensitive and responsive indicators of peroxisome proliferation, were slight compared with DEHP-induced changes but significant for 711P; relative liver weight and PCoA increased significantly at 1.2 and 2.5 percent in males and females. Small but statistically significant decreases in male serum cholesterol were reported at all doses and at the two high doses for male serum triglyceride levels. Responses to 711P in the other biochemical indicators of peroxisome proliferation were not significant. Relative kidney weights were slightly increased at the high dose in males and at the middle and high dose in females (Barber et al. 1987; CMA 1985).

711P was fed to Fischer 344 rats (10/sex/dose) in the diet for four weeks to provide daily doses of 0, 250, 500, 750, 1000, or 2000 mg/kg bw. Body weight gain in high-dose male rats was reduced significantly compared with controls beginning in the second week and continuing until study termination. The corresponding food consumption was only decreased in weeks 1 and 2. The only clinic effects observed were yellowed mottled livers in males receiving the three highest doses of 711P. Authors established a NOEL of 500 mg/kg/day for male rats, and 2000 mg/kg/day for females (Monsanto 1981).

The hepatotoxicity of 711P, a mixture of ~2/3 linear and 1/3 branched C₇, C₉, and C₁₁ alkyls, was evaluated along with five other phthalate diester compounds or mixtures (Smith et al. 2000). Male Fisher F344 rats (5/dose) were fed 1000 or 12,000 mg/kg bw phthalate diester and male B63F1 mice (5/dose) were fed 500 or 6000 mg/kg bw for two or four weeks. Biochemical indicators of hepatotoxicity were evaluated in both species: relative liver weight, peroxisomal beta oxidation (PBOX) level, gap junctional intercellular communication (GJIC), and DNA synthesis activity. PBOX activity was measured spectrophotometrically as the cyanide-insensitive reduction of NAD⁺ using palmitoyl-CoA as a substrate, GJIC was measured as the distance of *in situ* dye transfer through adjacent hepatocytes and DNA synthesis activity was the fraction of hepatocytes labeled with bromodeoxyuridine. The high dose of 711P produced a statistically significant ($p > 0.05$) increase in relative liver weights in male rats and mice after both two- and four-week exposures. Both species exposed to the high dose of 711P had elevated PBOX after two weeks, and mice, but not rats, retained the elevated activity at four weeks. In high-dose rats only, an inhibition of GJIC was measured at four weeks. At two weeks but not four, high-dose rats and low-dose mice had elevated periportal DNA synthesis activity (Smith et al. 2000).

Reproductive and Developmental Toxicity

No data on the reproductive or developmental toxicity of dinonyl phthalate, branched and linear were identified in a search of the literature. A reproductive toxicity pilot study and follow-up study of 711P (Santicizer® 711 Plasticizer) was conducted using Charles River COBS CD rats (Monsanto 1983a, 1983b). In the pilot study, pregnant rats (5/dose) received gavage doses of 0, 250, 500, 1000, 2500, or 5000 mg/kg/day 711P on gestational days (GD) 6–19, followed by sacrifice on GD 20. At the highest dose, there was a treatment-related effect on weight gain in dams and matted hair. Also at the highest dose, an increase in early resorptions accompanied by

a slight increase in post-implantation loss was reported. Similar results seen at 500 mg/kg/day were thought to be the result of a single test animal. For the pilot study, a maternal and reproductive NOAEL of 2500 mg/kg/day was determined (Monsanto 1983a).

In the follow up study, pregnant rats received gavage doses of 0, 250, 1000, or 5000 mg/kg/day 711P on gestational days (GD) 6–19, followed by sacrifice on GD 20. The only sign of maternal toxicity was matted hair in the high- and middle-dose groups. The maternal NOAEL was determined to be 5000 mg/kg/day. A statistically significant decrease in mean fetal body weight was reported at the high dose and is the basis for the 1000 mg/kg/day reproductive NOAEL. All other reproductive and developmental parameters measured (including numbers of corpora lutea, total implantations, early resorptions, post-implantation loss, viable fetuses, and litters with malformations) were not significantly different than control rats or historical species data, or did not show dose-related change (Monsanto 1983b).

Another reproductive toxicity study evaluated effects of 40, 200, or 1000 mg/kg bw 711P on Wistar rats. Pregnant rats (10/group) received doses on post-coitum days 6–15, and then were sacrificed on post-coitum day 20. In the high-dose group, signs of maternal toxicity included low mean body weights, body weight gain, and mean gravid uterus weights. Six of 10 rats showed vaginal hemorrhaging between days 15 and 20. Relative kidney and liver weights were statistically significantly higher than in control animals. Embryo-fetal toxicity manifested as drastically increased resorption rate (64.8 percent post-implantation loss), and decreased mean fetal body weights. External malformation rates were also higher; 9 of 53 fetuses in 5/7 litters showed such abnormalities (primarily acaudia or filiformed tail). No maternal or embryo/fetal-toxicity were reported at the other two dose levels (Anonymous 1992).

Genotoxicity

No genotoxicity data were identified for dinonyl phthalate, branched and linear in a search of the literature. However, three mutagenicity assays of 711P indicate that dinonyl phthalate, branched and linear is not mutagenic. The mutagenicity of 711P was tested in the Ames assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 in the presence and absence of a rat or mouse metabolic activation system. Concentrations of 0.01-10 μ L/plate 711P did not induce significant reverse mutations under any condition of this assay (Monsanto 1980).

A mouse lymphoma assay was performed under OECD Guideline 476 using 711P. Under conditions of metabolic activation, 125-1500 nL/mL 711P were tested, and in the absence of metabolic activation, 750-6000 nL/mL were tested. There was no significant increase in forward mutations in L5178Y cells in the absence of cytotoxicity under any conditions described here (Barber et al. 2000).

711P was also tested in the Balb/3T3 cell transformation assay in the absence of metabolic activation only. No significant increase in cell transformations was observed in Balb/c-3T3 mouse cells exposed to 711P at concentrations ranging from 0.063-6.32 μ L/mL. All appropriate negative and positive controls gave expected outcomes. Based on this assay, the 711P lacks the potential to be carcinogenic (Barber et al. 2000).

Carcinogenicity

Hirzy (1989) reported on a 1986 Monsanto bioassay in which Fisher-344 rats received 300, 1000, or 3000 ppm (0, 15, 50, or 150 mg/kg bw/day) 711P. Some liver neoplasia was reported in F-344 rats at the highest dose. However, Hirzy also stated that the diagnostics and methods used in the study were not easy to interpret, and other reviewers of the unpublished study have concluded that there is no evidence of treatment-related carcinogenicity. The tumor incidence table reported in Hirzy (1989) for 711P is reproduced below in Table 14.

Table 14: Bioassay Tumor Incidence Data for 711P (reported in Hirzy 1989)		
Dose group (ppm)	Female Rats	Male Rats
Control	17/72 ^{a**} ; 1/55 ^c	17/72 ^{a**} ; 0/68 ^d
300	6/14 ^{a*} ; 27/72 ^b ; 3/58 ^c	6/15 ^{a*} ; 32/72 ^b ; 7/69 ^d
1000	2/12 ^{a*} ; 26/71 ^b ; 2/59 ^c	2/10; 28/71 ^b ; 12/71 ^d
3000	8/72 ^{a**} ; 6/61 ^c	19/72 ^{a**} ; 4/71 ^d
a* = Neoplastic nodules + hepatocellular carcinomas; only livers with palpable tumor masses were examined; may count same animal twice a** = Neoplastic nodules + hepatocellular carcinomas; diagnostic criteria may have included preneoplastic foci b = Mononuclear cell leukemia c = Malignant mammary gland tumors d = Pancreatic islet cell adenomas		

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**Table 15: Summary of Toxicity Data for 1,2-Benzenedicarboxylic Acid, Dinonyl Ester, Branched and Linear
(CAS #68515-45-7)**

Organ/ System	Model	Exposure Route	Dose	Dose Duration	Endpoint	Effect	Reference
Liver	Fisher F344 rats	Dietary	<u>711P</u> : 0.6%, 1.2%, 2.5% (M: 652, 1294, 2604 mg/kg/day; F: 657, 1222, 2535 mg/kg/day)	21 days	NOEL < 652 mg/kg/day	0.6% and up: ↓ serum cholesterol (M) 1.2% and up: ↑ PCoA oxidation (M/F), ↑ relative liver weight (M/F); ↓ serum triglyceride (M); ↑ relative kidney wt (F) 2.5%: ↑ Peroxisome content (M), slight ↑ (F); ↑ relative kidney wt (M).	Barber et al. 1987; CMA 1985
Liver	Fischer 344 rats (10/sex/dose)	Dietary	0, 250, 500, 750, 1000, or 2000 mg/kg bw/day	4 weeks	NOEL = 500 mg/kg/day (M); = 2000 mg/kg/day (F)	<u>750 mg/kg/day and up</u> : discolored livers (M) <u>2000 mg/kg/day</u> : ↓Body weight gain (M) in absence of ↓ food consumption	Monsanto 1981
Liver	Fisher F344 rats	Dietary	<u>711P</u> : 1000 or 12,000 mg/kg bw	2 or 4 weeks	NOAEL = 1000 mg/kg bw	↑ Relative liver wts (2 and 4 wks); ↑ peroxisomal beta oxidation and ↑ periportal DNA synthesis activity (2 wks); ↓ gap junctional intercellular communication (4 wks)	Smith et al. 2000
Liver	B63F1 mice	Dietary	<u>711P</u> : 500 or 6000 mg/kg bw	2 or 4 weeks	NOEL = 500 mg/kg	↑ relative liver wts (2 and 4 wks); ↑ peroxisomal beta oxidation (2 and 4 wks)	Smith et al. 2000

Reproductive	Charles River COBS CD rats	Gavage	<u>711P</u> : 250, 500, 1000, 2500 or 5000 mg/kg/day 711P	GD 6-19	NOAEL _{reproductive} = NOAEL _{maternal} = 2500 mg/kg/day	Early resorptions, post-implantation loss; ↓ maternal weight gain	Monsanto 1983a
Reproductive	Charles River COBS CD rats	Gavage	<u>711P</u> : 0, 250, 1000, or 5000 mg/kg/day	GD 6-19	NOAEL _{reproductive} = 1000 mg/kg/day NOAEL _{maternal} = 5000 mg/kg/day	↓ mean fetal body wt	Monsanto 1983b
Reproductive	Pregnant Wistar rats (10/dose)	Gavage	<u>711P</u> : 40, 200, or 1000 mg/kg bw	Post-coitum days 6-15	NOAEL _{reproductive} = NOAEL _{maternal} = 200 mg/kg/day	Maternal toxicity: ↓ mean body wt, ↓ body wt gain, ↓ gravid uterus wt; vaginal hemorrhaging; ↑ rel kidney and liver wts. ↑ Resorption rate, ↓ fetal body wt; ↑ external malformation rates	Anonymous 1992
Systemic (neoplastic effects)	Fisher 344 rats (male and female)	Dietary	<u>711P</u> : 300, 1000, or 3000 ppm (15, 50, 150 mg/kg/day)	Chronic	Not determined	Liver neoplasia reported but results are widely discounted	Reported in Hirzy 1989

1,2-BENZENEDICARBOXYLIC ACID, NONYL UNDECYL ESTER, BRANCHED AND LINEAR (CAS #111381-91-0)

1,2-Benzenedicarboxylic acid, nonyl undecyl ester, branched and linear (CAS #111381-91-0), also called branched and linear nonyl undecyl phthalate, is an *ortho*-phthalate diester with side chains comprising primarily 9- and 11-carbon atoms each.

Acute Toxicity

An oral LD₅₀ value of >20 g/kg bw was derived in both mice and rats following single doses of Linevol® 9-11 phthalate, a mixture comprising approximately 20%/45%/35% by weight C9/C10/C11 phthalate diesters (Brown et al. 1970).

Irritation and Sensitization

Skin irritation by Linevol® 9-11 phthalate was evaluated in a covered assay using New Zealand white rabbits and in an uncovered assay using New Zealand white rabbits and albino guinea pigs. In rabbits, no irritation was observed in either covered or uncovered tests. In guinea pigs, the skin became coarse, slightly thickened, and some sloughing of surface layers was noted (Brown et al. 1970).

No ocular irritation was observed in rabbits exposed to Linevol 9-11 phthalate (Brown et al. 1970).

Skin sensitization was not induced by Linevol 9-11 phthalate when exposed to guinea pigs via topical administration or intradermal injection (Brown et al. 1970).

Systemic Toxicity

CFE rats (16-20/sex) were dosed with 5 mL/kg bw Linevol 9-11 phthalate for seven consecutive days. Some general depression (i.e. reduced activity level) was the only overt sign of toxicity. On the eighth day, rats were sacrificed and autopsied. Histological examination revealed periportal cytoplasmic vacuolation of the livers as a result of fat deposition. Authors concluded that this effect was due to the test substance, but not of toxicological significance (Brown et al. 1970).

There were no further toxicity, exposure, or use data identified for branched and linear nonyl undecyl phthalate. 1,2-Benzenedicarboxylic acid, nonyl undecyl ester, branched and linear comprises 1/6th of the phthalate ester mixture 711P (U.S. EPA 2001) and their toxicological properties are expected to be similar. Data describing the systemic and genetic toxicity of 711P are presented in this report under the section on dinonyl phthalate, branched and linear (CAS #68515-45-7).

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1,2-BENZENEDICARBOXYLIC ACID, DI-N-DECYL ESTER (CAS #84-77-5)

1,2-Benzenedicarboxylic acid, di-n-decyl ester, also called di-n-decyl phthalate (DnDP) is a linear ortho-phthalate diester comprising two 9-carbon backbones. DnDP was listed by the U.S. EPA as a High Production Volume (HPV) chemical in 1990, indicating production and/or importation into the United States was in excess of 1 million pounds. The U.S. EPA's Inventory Update Reporting (IUR) lists 1 to 10 million pounds were produced or imported in to the United States in 2001 (U.S. EPA 2002).

Exposure

Occupational exposure to di-n-decyl phthalate may occur through inhalation and dermal contact with this compound at workplaces where di-n-decyl phthalate is produced or used. Use data indicate that the general population may be exposed to di-n-decyl phthalate via inhalation of particulates and dermal contact with consumer products containing di-n-decyl phthalate (HSDB 2010).

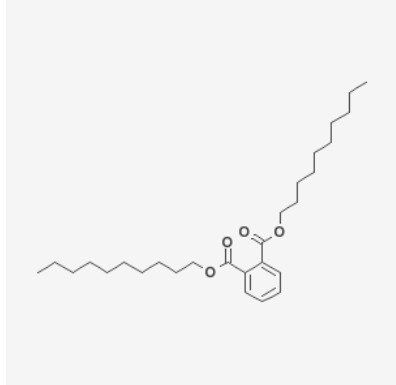
At least one biologics company (Terumo Corporation of Tokyo, Japan) has used DnDP as a plasticizer in a polyvinyl chloride (PVC) blood bag; it is not clear where in the world the bag is sold and used. Human exposure to DnDP may occur via migration into blood. The concentration of DnDP extracting into the plasma of blood platelet concentrates after a five-day storage was low (0.58 ± 0.06 mg/bag), about $1/80^{\text{th}}$ that of di-(2-ethylhexyl)phthalate. Morphological changes of platelets into spherical forms with dendrites were more frequently observed in PVC-DnDP bags than in PVC-di-(2-ethylhexyl) phthalate bags (Shimizu et al. 1989).

The UK's Food Safety Directorate (now the Food Standards Agency) carried out a survey of the levels of total and individual phthalates in samples of composite fatty foods from a total diet study. The survey was carried out using stored samples of food, including carcass meat, meat products, offals, poultry, eggs, fish, fats, oils, milk, and milk products that had been collected in 1993. Di-n-decyl phthalate was not detected (limit of detection = 0.001 mg/kg) in any of the samples analyzed (MAFF 1996). No parallel survey that included di-n-decyl phthalate was identified for U.S. foods.

Physicochemical Properties

Names and synonyms, registry numbers, molecular structure, and other physicochemical characteristics of di-n-decyl phthalate are summarized below in Table 16.

Table 16: Physicochemical Properties of Di-n-decyl Phthalate	
Identification	Information
Chemical Name	Di-n-decyl phthalate
Synonyms	1,2-Benzenedicarboxylic acid, di-n-decyl ester; Bis(n-decyl) phthalate; Decyl phthalate; Didecyl phthalate;

	Di-n-decyl 1,2-Benzenedicarboxylate; Phthalic acid, di-n-decyl ester; Vinicizer 105; Vynsize 105; 1,2-Benzenedicarboxylic acid, 1,2-di-n-decyl ester
CAS Number	84-77-5
Structure	
Chemical Formula	C28-H46-O4
Molecular Weight	446.663
Physical State	Viscous liquid
Color	Light-colored to colorless
Melting Point	2.5°C
Boiling Point	261°C @ 5 mm Hg
Vapor Pressure	7.89×10^{-9} mm Hg @25°C (est.)
Water Solubility	2.2×10^{-4} mg/L @25°C
Log K _{ow}	9.05
Flashpoint	232°C
Source: HSDB 2010	

Toxicokinetics

No data on the toxicokinetics of di-n-decyl phthalate were identified in a search of the literature.

Acute Exposure

As with other phthalate esters, the acute toxicity of DnDP is low in multiple exposure scenarios. In rats, a single oral DnDP dose of >64 mL/kg body weight (bw) (62,000 mg/kg⁴) was not fatal (Smyth et al. 1962). A dermal LD₅₀ value of 16,300 mg/kg bw was determined in albino New Zealand rabbits (Smyth et al. 1962). The LD_{Lo} of DnDP was 2233 mg/kg bw in mice dosed intraperitoneally; effects at this dose included ptosis and somnolence (Nematollah et al. 1967). Intravenous (i.v.) administration of 16,000 mg/kg DnDP produced lethality in all mice receiving this dose, while a 10,500 mg/kg bw i.v. dose produced no lethality (Shimzu et al. 1989). No fatalities occurred after a 650 mg/kg bw i.v. dose of DnDP to rabbits, but blood pressure was decreased and respiration increased in rats (Woodward et al. 1986).

⁴ Specific gravity di-n-decyl phthalate = 0.97 g/cm.³

Irritation and Sensitization

The available data suggest that DnDP is not a dermal irritant. Primary skin irritation tested on the abdomen of albino rabbits rated 2 out of 10, indicating very mild irritation (Smyth et al. 1962). In addition, no reports of dermal sensitization in humans have been identified (Woodward et al. 1986).

Di-n-decyl phthalate is not expected to be a significant eye irritant. After a 24-hour exposure, DnDP ocular irritation in rabbits rated 2 on a scale of 10, where 1 is the lowest degree of corneal injury (Smyth et al. 1962).

Systemic Toxicity

No sign of toxicity was observed in chickens given DnDP doses of 970 mg/kg bw on five consecutive days. Daily doses of 1940 mg/kg bw DnDP given to cats for 12 weeks did not give rise to any physiological or biological adverse effects (reported in Lefaux 1968). No further details were available for either study.

Adult male Wistar rats received intragastric doses of 5.0 mmol/kg/day (2233 mg/kg/day) di-n-decyl-, dibutyl-, di(2-ethylhexyl)-, or di(3,3,5-trimethylhexyl)-phthalate for six days. Following sacrifice, livers were removed and microsomes extracted for analysis. In a parallel experiment, hepatocytes were incubated with di-n-decyl phthalate (or one of the other phthalates) at a final concentration of 2.0 mM. DnDP produced a significant increase in the amount of microsomal cytochrome P-450 *in vivo* with no accompanying changes in the activities of ethoxycoumarin deethylase or aryl hydrocarbon hydroxylase, which are dependent on cytochrome P-450. *In vitro* the activities of these two enzymes were similarly unaffected by DnDP. Epoxide hydratase activity, but not glutathione S-transferase activity, increased significantly in the presence of DnDP *in vivo*; neither enzyme responded to the chemical *in vitro*. Glucuronide conjugation of o-aminophenol was enhanced *in vitro* in the presence of di-n-decyl phthalate (Aitio and Parrki 1978).

Reproductive and Developmental Toxicity

No data on the reproductive or developmental toxicity of di-n-decyl phthalate were identified in a search of the literature.

Genotoxicity

No studies were identified in the literature search that reported on the mutagenicity or clastogenicity of didecyl phthalate. Sato et al. (1994) investigated the ability of DnDP to enhance or suppress the mutagenicity of the amino acid pyrolysate 3-amino-1-methyl-5H-pyrido-[4,3-b]indole (Trp-2) in the SOS chromotest. DnDP did not affect the mutagenicity of Trp-2 in *Escherichia coli* PQ37 under the conditions of this assay.

Carcinogenicity

No data on the carcinogenicity of di-n-decyl phthalate were identified in a search of the literature.

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1,2-BENZENEDICARBOXYLIC ACID, DI-C6-10-ALKYL ESTERS (CAS #68515-51-5)

1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters (di-C6-10 alkyl phthalates) is a mixture consisting of several phthalates each with two linear ester side chains consisting of 6 to 10 carbon atoms (C6-10). The mixture is typically 79 percent di-n-decyl phthalate (DnDP, CAS #84-77-5), 20 percent di-n-octyl phthalate (DnOP, CAS #117-84-0), and 1 percent di-n-hexyl phthalate (DnHP, CAS #84-75-3) (NICNAS 2008), and therefore, can be classified as a high molecular weight phthalate ester, based on U.S. EPA (2001) guidelines.

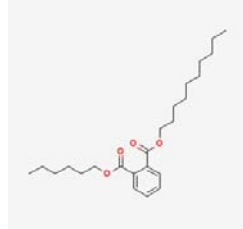
Di-C6-10 alkyl phthalates is a primary plasticizer for polyvinyl chloride (PVC) resins intended for use in the manufacture of flooring and carpet tile, canvas tarpaulins, swimming pool liners, notebook covers, traffic cones, toys, vinyl gloves, garden hoses, weather stripping, flea collars, and shoes. Fifty million pounds of di-C6-10 alkyl phthalates were produced in the United States in 1994 (NICNAS 2008).

Exposure

Exposure to 1,2-benzenedicarboxylic acid, di-C6-10-alkyl esters is anticipated in occupational settings where this substance is manufactured or used to produce a consumer product.

Physicochemical Properties

The physicochemical properties of di-C6-C10 alkyl phthalates are summarized below in Table 17.

Table 17: Physicochemical Properties of 1,2,-Benzenedicarboxylic Acid, Di-C6-10 Alkyl Esters	
Identification	Information
Chemical Name	Di-C6-10-alkyl phthalates
Synonyms	Di(C6-C10)alkyl phthalate; 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters; 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters; Di-(hexyl, octyl, decyl) phthalate; Linplast 610P; Witamol 110; ALFOL 6-10 Phthalate
CAS Number	68515-51-5
Structure	 (one of several possible structures)
Chemical Formula	C ₂₇ H ₄₄ O ₄ (Based on C6/C10)
Molecular Weight	334.5 – 446.7

Physical State	Liquid
Melting Point	-50°C - -16°C
Boiling Point	250°C @ 5 hPa
Vapor Pressure	< 0.001 hPa @ 20°C
Water Solubility	< 0.2 mg/L @20°C
Log K _{ow}	8.2
Flashpoint	230°C
Source	ECB 2000 (unless otherwise stated)

Toxicokinetics

There were no data identified on the toxicokinetics of di-C6-10 alkyl phthalates.

Acute Toxicity

Like its component phthalates, the acute toxicity of di-C6-C10 alkyl phthalates in animal tests is low via oral, inhalation, and dermal exposure routes. An oral LD₅₀ value of >2000 mg/kg di-C6-10-alkyl phthalates has been established in male and female rats under OECD Guideline 401. No adverse effects were observed. Likewise, an acute oral toxicity test of ALFOL 6-10 Phthalate, a commercial di-C6-C10 alkyl phthalate, determined a LD₅₀ value of >30,720 mg/kg bw in male and female rats following a single exposure and two-week recovery period. In an 8-hour inhalation exposure, no deaths were reported among rats in a saturated atmosphere of di-C6-10-alkyl phthalates. A dermal LD₅₀ of >20,000 mg/kg bw was established in rabbits for di-C6-C10 alkyl phthalates (method not specified) (ECB 2000).

Irritation and Sensitization

Di-C6-10-alkyl phthalates rated 2 on a scale of 10 in a primary dermal irritation index in rabbits, where 1 is the lowest degree of irritation. Further details of this index and results were not available. Under OECD Guideline 404, the acute index of dermal irritation/corrosion in rabbits was 1.25 out of 8 for di-C6-10-alkyl phthalates, garnering a rating of “not irritating.” Likewise, ALFOL 6-10 phthalate was not irritating to rabbit skin in the Draize Test (ECB 2000).

Under OECD Guideline 405, rabbits were exposed to undiluted di-C6-10-alkyl phthalates on the eye. The test substance was not an ocular irritant. The EC classification of this substance in another Draize eye test was “not irritating,” although the classification under the Draize test itself was “slightly irritating.” A third eye irritation assay rated this compound 1 out of 10 in a primary irritation index (ECB 2000).

No dermal or respiratory sensitization data were identified for di-C6-10-alkyl phthalates. The European Chemicals Bureau used data for di-n-octyl phthalate as “read across” data in the IUCLID dataset for di-C6-10-alkyl phthalates. Di-n-octyl phthalate was sensitizing to the skin in a human patch test (ECB 2000).

Systemic Toxicity

Male and female Fisher 344 rats (5/sex/dose) were fed 0, 0.6, 1.2, or 2.5% 610P, a phthalate ester mixture comprising C6, C8, and C10 diesters, in the diet for 21 days. The doses are approximately equivalent to 652, 1294, and 2604 mg/kg/day for males, and 657, 1222, and 2535 mg/kg/day for female rats. No treatment-related changes were observed in body weights, food intake, or testes or kidney weights. In both sexes at all doses, there were increases in absolute and relative liver weights. Decreased cytoplasmic basophilia was observed in hepatocytes of high-dose females, and in one female of the 1.2 percent dose group. In males, this was not observed, although it may have been obscured by extensive lipid deposition in hepatocytes, which was accompanied by slightly increased mitotic activity and cell necrosis. Serum cholesterol and triglyceride levels showed nondose-related changes in both sexes. Rats receiving the high dose of 610P showed slight (males) to moderate (females) increases in peroxisome numbers. High-dose males and females, as well as males at 1.2 percent showed significantly increased cyanide-insensitive palmitoyl CoA oxidation. Lauric acid 12-hydroxylase activity was increased at the 2.5 percent dietary dose for both sexes, and the 11-hydroxylase activity was significantly increased in all treated females (Barber et al. 1987). A NOAEL cannot be established from results of this study because there were significant liver effects even at the lowest dose of 652–657 mg/kg/day.

In a two-generation reproductive/developmental toxicity study, Sprague-Dawley rats (24/sex/group) were fed 0, 1000, 3000, or 10000 ppm (approximately 45, 135, and 450 mg/kg bw/day) di-C6-10 alkyl phthalates in the diet 10 weeks prior to and throughout the mating, gestation, and lactation period (Condea Vista 1998). Systemic effects on the F0 generation are presented here, and reproductive and developmental effects are described in the next section, under the Reproductive and Developmental Toxicity heading.

Toxicity to the F0 generation included decreased body weight gain and food consumption at the high dose. Liver weights were statistically increased for high- and middle-dose rats of both sexes. Absolute liver weight was also increased in F0 females at the low dose, but relative liver weight was not statistically significantly different than controls for these animals. Mean relative kidney weights of females were increased in the top two dose groups. At necropsy, most high-dose adult rats had gross changes in the liver, including discoloration/paleness, enlargement with prominent lobulation, and/or pale/dark foci. Pale liver foci were also observed in some males at 3000 ppm. Most F0 males at 10000 ppm had histological changes in the liver, including basophilic foci, eosinophilic cell foci, clear cell foci, vacuolation, bile duct hyperplasia, and Kupffer-cell pigmentation (Condea Vista 1998). The NOAEL for systemic parental effects was determined to be 1000 ppm (~45 mg/kg/day) based on liver and kidney weight changes at 3000 ppm.

A mixture of phthalate esters derived from hexanol and octanol (DA68P) and another mixture derived from heptanol and nonanol (DA79P) were applied as a neat liquid to the skin of rats and mice for 10 days. DA68P exposure resulted in the deaths of 50 percent of the mice, while DA79P produced no overt signs of toxicity. In rats, leucocytosis was noted, and there was hyperaemia at the site of application of both phthalate mixtures. Doses were not specified. In another experiment from the same author, DA68P and DA79P were applied to the dorsal surface of an unnamed rodent species at 10, 100, or 500 mg/kg bw/day for five months. No effects were seen from DA79P. At the middle dose, DA68P produced dermal irritation, and at the high dose, 50 percent of the rodents died with 5–23 applications (reported in Woodward et al. 1986).

The composition of di-C6-10 alkyl phthalate is typically 79 percent C10 phthalate, 20 percent C8 phthalate, and 1 percent C6 phthalate (NICNAS 2008). Because the content of di-C6-10 alkyl phthalate favors the heavier end of this phthalate range, and the subacute dermal toxicity studies implicate the C6-8, rather than the C7-9 dialkyl phthalates, in adverse effects and lethality, the studies reported by Woodward et al. may not be the most accurate predictors of the toxicity of di-C6-10 alkyl phthalate.

Reproductive and Developmental Toxicity

A one-generation developmental toxicity study of the commercial di-C6-10 alkyl phthalate ester Witamol 110/Linplast 610P was carried out using Sprague-Dawley rats (Condea Vista 1996). Pregnant rats (25/dose) received gavage doses of 0, 100, 500, or 1000 mg/kg/day of Witamol 110/Linplast 610P during gestation days (GD) 6–16. On GD 20, they were killed, and the live fetuses were examined for developmental abnormalities. The study authors assigned a developmental NOEL of 100 mg/kg/day based on an increased number of fetuses with 14th ribs at the middle and high doses, and an increased number of retarded sternebrae at the high dose only. Maternal effects at the high dose were slight body weight and food consumption increases and slight piloerection. Study authors assigned a maternal NOEL of 500 mg/kg/day based on these minor effects.

In a two-generation study, Sprague-Dawley rats (24/sex/group) were fed 0, 1000, 3000, or 10000 ppm (approximately 45, 135, and 450 mg/kg bw/day) Witamol 110/Linplast 610P, a commercial di-C6-10 alkyl phthalate ester (Condea Vista 1998). The test substance was administered in the diet 10 weeks prior to mating, and then throughout the mating, gestation and lactation periods. F1 animals received the parental diet at weaning for the subsequent 11 weeks, and then throughout mating, gestation, and lactation. Selected F2 animals were treated into adulthood until termination. The reproductive and developmental effects of Witamol 110/Linplast 610P are presented here. Systemic effects on the F0 generation were described previously under the Systemic Toxicity section.

At the high dose, reductions in weight gain were reported for F1 and F2 adult males, and food consumption was reduced for F1 males and for females during lactation. Liver weights were statistically higher for high-dose female rats of both generations and for F2 males, for mid-dose F2 rats of both sexes, and for F1 females receiving the low dose. Mean relative kidney weights of F1 females were increased at all three doses. Absolute, but not relative kidney weights in F1 males were increased at 10000 and 3000 ppm. At necropsy, most high-dose adult rats of each generation had gross changes in the liver, including discoloration/paleness, enlargement with

prominent lobulation, and/or pale/dark foci. Pale liver foci were also observed in some males at 3000 ppm in all the generations. Most F1 males at 10000 ppm had histological changes in the liver, including basophilic foci, eosinophilic cell foci, clear cell foci, vacuolation, bile duct hyperplasia, and Kupffer-cell pigmentation.

High-dose F1 males had significantly reduced (weanling) then greater (in adulthood) adjusted testes weights compared to controls; their prostate weight in adulthood was significantly lower compared with controls. The absolute seminal vesicle weight was significantly reduced in high-dose males of all three generations, as were the adjusted seminal vesicle weights of high-dose F1 and F2 adult males. A similar observation was made on F2 adults receiving 3000 ppm, but the effect was not considered treatment-related, since it was absent in other generations. According to NICNAS (2000), the seminal vesicle weight changes were related to body weight decreases resulting from reduced food intake. Overall, study authors concluded that the effects on reproductive organs, liver, and kidney were similar across generations, and therefore, not specifically reproductive effects.

There were no obvious effects of treatment on the mating performance, fertility indices, or the duration of gestation. There was no effect on absolute testis weight, seminiferous tubule diameter, or on qualitative measures of spermatogenesis in treated animals. Developmental toxicity at the high dose included decreased litter size and survival from post-natal day 4 through 21 in offspring of both F0 and F1 generations; decreased litter and pup weights in both generations; increased adjusted body weights for F1 adult rats; and decreased weanling weights. A significant delay in sexual maturity, as measured by preputial separation, was evident at the high dose when the two generations were taken together.

The NOAEL for reproductive effects was 3000 ppm (135 mg/kg bw/day) based on delayed sexual maturity. The NOAEL for developmental effects was also considered to be 3000 ppm (135 mg/kg bw/day) because of slightly decreased litter survival and pup and litter weights at the highest dose tested. A NOAEL for systemic offspring toxicity could not be established due to increased liver and kidney weights among F1 females at 1000 ppm (45 mg/kg bw/day), the lowest dose tested (Condea Vista 1998).

Genotoxicity

Esters 610P, a phthalate ester mixture comprising C6, C8, and C10 diesters was tested for mutagenicity in the mouse lymphoma assay. L5178Y (TK+/TK-) cells were exposed to 610P at 0.5-5.0 µL/mL or 0.15-0.40 µL/mL in the absence or presence, respectively, of activated S-9 fraction derived from rat liver. The C6, C8, C10 phthalate ester mixture produced equivocal results. A significant increase in mutant frequency was observed at 0.5-3.0 µL/mL in the absence of activation, but no such increase was seen at 4.0 or 5.0 µL/mL. With metabolic activation, 8 of 10 trials were positive for mutagenicity; one replicate each at 0.15 and 0.2 µL/mL 610P was negative. The pattern of results was reproducible, but no relationship with dose or toxicity could be discerned (Barber 2000).

In the same study, the neoplastic potential of 610P (purity = 99.8 percent) was evaluated using a standard *in vitro* transformation assay in Balb/c-3T3 A-31 mouse cells in the absence of metabolic activation. Concentrations of 0.1-1.0 µL/mL 610P did not induce a statistically

significant increase in the number of transformed foci in mouse cells (Barber 2000). Another transformation assay had similar results at 610P concentrations of 63 - 6320 nL/mL (CMA 1985). Based on these assays, 610P lacks the potential to be carcinogenic.

None of the three constituents of di-C6-10 alkyl phthalates, DnHP, DnOP or DnDP, was genotoxic in *in vitro* studies (NICNAS 2008).

Carcinogenicity

As described in the previous section, two independent *in vitro* transformation assays using Balb/c-3T3 A-31 mouse cells failed to show any evidence of carcinogenic potential (Barber 2000; CMA 1985).

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**Table 18: Summary of Toxicity Data for 1,2-Benzenedicarboxylic Acid, Di-C6-10 Alkyl Phthalates
(CAS #68515-51-5)**

Organ	Model	Exposure Route	Dose	Dose Duration	Endpoint	Effect	Reference
Liver	Fisher 344 rats	Dietary	610P: 0.6, 1.2, or 2.5%	21 days	NOAEL <0.6% (652 mg/kg/day)	<p><u>0.6%</u>: ↑ abs and rel liver wts (M/F); ↑ 11-hydroxylase activity (F)</p> <p><u>1.2%</u>: ↑ cyanide-insensitive palmitoyl CoA oxidation (M); ↑ 11-hydroxylase activity (F)</p> <p><u>2.5%</u>: ↓ cytoplasmic basophilia (F); non-dose related changes in serum cholesterol and triglyceride levels (M/F); slight (M) to moderate (F) ↑ in peroxisome numbers; ↑ cyanide-insensitive palmitoyl CoA oxidation (M/F); ↑ lauric acid 12-hydroxylase activity (M/F)</p>	Barber et al. 1987
<u>Developmental (1 Generation)</u>	<u>Pregnant Sprague-Dawley rats (25/dose)</u>	Gavage	<u>0, 100, 500, or 1000 mg/kg/day</u>	<u>GD 6-16</u>	<p>NOEL_{developmental} = 100 mg/kg/day</p> <p>NOEL_{maternal} = 500 mg/kg/day</p> <p>NOAEL_{maternal} >1000 mg/kg/day</p>	<p><u>500 mg/kg/day</u>: ↑ no. fetuses with 14th rib.</p> <p><u>1000 mg/kg/day</u>: ↑ no. fetuses with retarded sternebrae; ↑ maternal body wt and food consumption, slight piloerection.</p>	<u>Condea Vista 1996</u>
Reproductive/ Developmental (2 Generation)	Sprague-Dawley rats	Dietary	0, 1000, 3000, or 10000 ppm (~ 45, 135, 450 mg/kg bw/day)	<p><u>F0</u>: 10 wks prior to and throughout mating, gestation and lactation;</p> <p><u>F1</u>: at</p>	<p>NOAEL_{parental} = 135 mg/kg/day</p> <p>NOAEL_{systemic (offspring)} < 45 mg/kg bw/day</p> <p>NOAEL_{reproductive}</p>	<p><u>45 mg/kg/day</u>: ↑ liver and kidney wts (F1 F)</p> <p><u>135 mg/kg/day</u>: ↑ liver wts (F0 and F2 M/F); ↑ relative kidney wt (F1 F); ↑ absolute kidney wts (F1 M)</p> <p><u>450 mg/kg/day</u>: ↑ liver wts (F, all</p>	Condea Vista 1998

				weaning, +11 weeks, +throughout mating, gestation and lactation	= NOAEL _{developmental} = 135 mg/kg bw/day	gens/ F0 and F2 M); ↑ rel kidney wt (F1 F); ↑ abs kidney wts (F1 M); gross liver changes (M,F); histological liver changes (F0 and F1 M); ↓ adj testis wt (F1); ↓ prostate wt (F1); ↓ abs seminal vesicle wt (all gens), ↓adj seminal vesicle wts (F1 and F2); ↓ litter size; ↓ survival PND 4 to 21; ↓ pup wts; delay in sexual maturity, (preputial separation); ↑ adj body wts (F1 adults); and ↓weanling wts	
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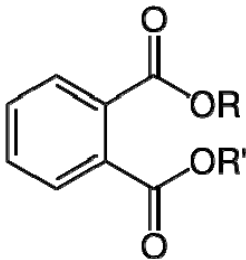
1,2-BENZENEDICARBOXYLIC ACID, MIXED DECYL AND HEXYL AND OCTYL DIESTERS (CAS #68648-93-1)

1,2-Benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters (CAS #68648-93-1) is an *ortho*-phthalate diester with side chains comprising a mixture of primarily 6-, 8- and 10-carbon atoms. It falls into the U.S. EPA's high molecular weight phthalate ester category (U.S. EPA 2006).

1,2-Benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters is also called 610P (U.S. EPA 2006) and is nearly identical in structure to 1,2-benzenedicarboxylic acid, di-C6-10-alkyl esters (CAS #68515-51-5). Toxicity data on this 1,2-benzenedicarboxylic acid, di-C6-10-alkyl esters are presented previously in this report and should be referenced as read across data for 1,2-benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters.

Physicochemical Properties

Some physicochemical properties of 1,2-benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters are listed below in Table 19.

Table 19: Physicochemical Properties of 1,2-Benzenedicarboxylic Acid, Mixed Decyl and Hexyl and Octyl Diesters	
Identification	Information
Chemical Name	1,2-Benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters
Synonyms	Mixed hexyl, octyl, decyl phthalates; Phthalic acid mixed decyl and hexyl and octyl diesters; Phthalic anhydride, hexyl, octyl, decyl esters (ChemIDPlus 2010); Palatinol 610P (BASF 2009); 610P
CAS Number	68648-93-1
Structure	 R or R' = C ₆ H ₁₃ or C ₈ H ₁₇ or C ₁₀ H ₂₁
Chemical Formula	C ₂₄ H ₃₈ O ₄ (based on C6/C10)
Molecular Weight	334.5 – 446.7
Melting Point	-45°C
Boiling Point	431°C
Vapor Pressure	1.33x10 ⁻⁷ hPa @25°C

Water Solubility	0.00088 mg/L @25°C
Log K _{ow}	8.17
Source	U.S. EPA 2006

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1,2-BENZENEDICARBOXYLIC ACID, DI-C7-9 BRANCHED AND LINEAR ALKYL ESTERS (CAS #68515-41-3)

1,2-Benzenedicarboxylic acid di-C7-C9-phthalate, branched and linear (CAS #68515-41-3) is a phthalate ester mixture derived from alcohols with 7–9 carbon atoms. It has been used as a plasticizer for polyvinyl chloride, and in food packaging polymers that contact aqueous food types (Gaunt et al. 1968). The U.S. EPA HPV considers this compound to be a high molecular weight phthalate, as 90 percent or more of the phthalate ester carbon chains are $\geq C7$ (U.S. EPA 2001).

Exposure

Exposure to 1,2-benzenedicarboxylic acid, di-C7-C9-phthalate, branched and linear is anticipated in occupational settings where this substance is manufactured or used to produce a consumer product.

Physicochemical Properties

The physicochemical properties of 1,2-benzenedicarboxylic acid di-C7-C9-phthalate, branched and linear are summarized below in Table 20.

Table 20: Physicochemical Properties of 1,2,-Benzenedicarboxylic Acid, di-C7-C9 Phthalate, Branched and Linear	
Identification	Information
Chemical Name	Di-C7-C9 phthalates, branched and linear
Synonyms	1,2-Benzenedicarboxylic acid, di C7-C9 alkyl ester, branched and linear; Dialkyl 79 phthalate; Alphanol 79 phthalate
CAS Number	68515-41-3
Structure	<p>R or R' = C₇H₁₅, C₈H₁₇, or C₉H₁₉ (branched or linear)</p>
Chemical Formula	C ₂₄ H ₃₈ O ₄ (based on C8 length)
Molecular Weight	362.5 – 418.6
Melting Point	-48°C - -45°C (NICNAS 2008)

Boiling Point	226 °C 398 – 454°C (NICNAS 2008)
Vapor Pressure	0.001 hPa @ 100°C
Water Solubility	<1 mg/L 6.1 x 10 ⁻⁷ – 170 x 10 ⁻⁷ g/L (NICNAS 2008)
Log K _{ow}	6.9 – 8.6
Flashpoint	246°C
Source	ECB 2000 (unless otherwise stated)

Toxicokinetics

There were no data identified on the toxicokinetics of di-C7-C9 alkyl phthalates, branched and linear.

Acute toxicity

An oral LD₅₀ value of >19,300 mg/kg bw was derived in both mice and rats following single doses of Linevol® 7-9 phthalate, an 80% linear phthalate ester mixture comprising approximately 45%/40%/15% by weight C7/C8/C9 phthalate diesters. The only physical observation made of these rats was persistently wet fur in the perianal area at unspecified dose levels (Brown et al. 1970). Rodents showed signs of excitement, lethargy, paresis of the extremities, muscular tensions, and reductions in rate of body weight gain after 6000–15,000 mg/kg bw doses of dialkyl 79 phthalate (Woodward et al. 1986). An oral LD₅₀ of >10,000 mg/kg bw of the Exxon product MRD-81-20 (identified as CAS #68515-41-3) was determined in Sprague-Dawley albino rats (Exxon Chem. 1981).

A single dermal application of 2000, 4000, or 6000 mg/kg neat di-C7-C9 phthalate had no toxic effects on rats or mice (ECB 2000). Male and female New Zealand albino rabbits (2/sex/dose) with 20 percent shaved body hair were exposed to the Exxon product MRD-81-20 (identified as CAS #68515-41-3) at 50, 200, 794, or 3160 mg/kg bw for 24 hours with an occlusive patch. Exposure was followed by a 14-day observation period. There was no mortality in any dose group, so the dermal LD₅₀ was determined to be greater than 3120 mg/kg bw. A dose-dependent increase in the severity of erythema was noted, reaching a severe level in some animals at the highest dose after 24 hours and 3 days, and then almost disappearing again by day 7 (Exxon Chem. 1982a).

Dialkyl 79 phthalate had an intraperitoneal (i.p.) LD₅₀ >20,000 mg/kg bw in rats and mice. Overt effects following i.p. dosing were mild diarrhea and oily, matted fur (Gaunt et al. 1968).

Irritation and Sensitization

Skin irritation by Linevol® 7-9 phthalate was evaluated in a covered assay using New Zealand white rabbits and in an uncovered assay using New Zealand white rabbits and albino guinea pigs. In rabbits, no irritation was observed in either covered or uncovered tests. In guinea pigs, the

skin became coarse, slightly thickened, and some sloughing of surface layers was noted (Brown et al. 1970).

In a Draize ocular irritation assay, six albino New Zealand rabbits were exposed to the Exxon product MRD-81-20 (CAS #68515-41-3) via the eye. This product produced no signs of irritation after 24, 48, or 72 hours (Exxon Chem. 1982b). In addition, no ocular irritation was observed in rabbits exposed to Linevol 7-9 phthalate (Brown et al. 1970).

Skin sensitization was not induced by Linevol 7-9 phthalate when exposed to guinea pigs via a 3-day open dermal exposure or intradermal injection of a 0.1 percent solution (Brown et al. 1970). The induction was followed by 10 days without treatment, a 48-hour dermal challenge, and then a repeat of the entire test. The test substance was not sensitizing under these conditions. Additionally, no sensitization was observed after a 21-day epicutaneous/challenge test in guinea pigs using neat or 10 percent unspecified "test substance" (ECB 2000).

Systemic Toxicity

CFE rats (16-20/sex) were dosed via intragastric intubation with 5 mL/kg bw Linevol 7-9 phthalate for seven consecutive days. Some general depression was the only overt sign of toxicity. On the eighth day, rats were sacrificed and autopsied. Histological examination revealed periportal cytoplasmic vacuolation of the livers as a result of fat deposition. Authors concluded this effect was due to the test substance, but not of toxicological significance (Brown et al. 1970).

Shell Chemical's dialkyl 79 phthalate, derived from 77 percent linear (37 percent C7, 26 percent C8, and 14 percent C9) and 23 percent branched alcohols (8 percent C7, 9 percent C8, and 6 percent C9), was evaluated for hepatic and testicular toxicity. Six Wistar rats/sex received 0 or 2500 mg/kg bw/day dialkyl 79 phthalate for 7 or 21 days via gavage. Effects of the single dose after 7 days included liver enlargement and liver enzyme changes in both sexes and decreased body weight gain and changes in liver structure in males. After 21 days, male rats showed decreased growth, lower testis weight, along with bilateral tubular atrophy, liver enlargement, decreases in liver enzyme activities (succinate dehydrogenase, 7-ethoxycoumarin o-deethylase, aniline 4-hydroxylase, glucose-6-phosphatase, alcohol dehydrogenase, microsomal protein content, and cytochrome P-450), and in the hepatocytes observations included cloudy swelling, fatty vacuolation, condensed nuclei, and degenerate mitochondria. In female rats, effects observed after 21 days were increased body weight gain, enlarged liver, depressed hepatic cytochrome P450 and glucose-6-phosphatase activities, and increased alcohol dehydrogenase activity; hepatocyte effects included cloudy swelling and fatty vacuolation. No effects on behavior were noted (Mangham et al. 1981).

The testicular atrophy produced by dialkyl 79 phthalate is interesting in light of a study by Foster et al. (1980), which described no testicular effects after a 4-day exposure in rats to di-n-heptyl and di-n-octyl phthalates at 2600 and 2800 mg/kg/day, respectively. Presumably, testicular toxicity of this mixture is derived from one of the branched components, or a metabolite whose effects were not observed after only 4 days (Mangham et al. 1981).

Dialkyl 79 phthalate was fed to CFE strain rats (15/sex/dose) at 0.125, 0.25, 0.5, or 1.0 percent in the diet in a 90-day toxicity test (Gaunt et al. 1968). Extensive gross and histopathological examinations and urinalysis established a NOEL of 0.125 percent (~60 mg/kg/day) based on decreased hemoglobin levels, red blood cell counts, and increased urinary cell excretion. At the highest two doses, liver and kidney weights were increased and hematocrit, hemoglobin, and red blood cell counts were significantly reduced. At the highest dose only, male growth rate was reduced, urine concentration was abnormal, and relative brain and gonad weights were significantly higher. In both sexes, the level of hemosiderin in the spleen was elevated.

One male and one female New Zealand white rabbit were exposed to a neat 1.0 mL dermal dose of an 80 percent linear phthalate ester mixture comprising 45 percent C7, 40 percent C8, and 15 percent C9 (w/w) 5 days/week for 3 weeks. Visual and histopathological examination indicated no toxic effects or irritation following this exposure regime. The same methodology was carried out on five albino guinea pigs of each sex, except that they received a 0.5 mL application of neat test substance. Dermal exposure in guinea pigs resulted in coarse, thickened skin with some superficial sloughing (Brown et al. 1970).

Reproductive and Developmental Toxicity

Bisoflex L79P (“D79P”), a plasticizer with a typical carbon chain distribution of 39–50 percent C7, 17–28 percent C8 and 27–39 percent C9, was administered to Sprague-Dawley rats in a two-generation reproductive toxicity test (Willoughby et al. 2000). The parental generation (F0) was fed 0, 0.1, 0.5, or 1.0%⁵ D79P continuously over two generations. The test substance was administered in the diet 10 weeks prior to mating and then throughout the mating, gestation and lactation periods. Select F1 animals received the parental diet at weaning, and then throughout mating, gestation, and lactation. They were sacrificed along with F2 generation animals on post-natal day (PND) 25.

Reproductive parameters were largely unaffected by treatment with D79P in both F0 and F1 generations. Gestation duration distribution in the F0 generation was slightly but significantly reduced by the high dose of D79P. The female offspring of the high-dose F0 generation had significantly reduced body weights on PNDs 14, 21, and 25, as did those of high-dose F1 animals on PND 25. Parameters showing no treatment-related effects included: mating success, precoital interval, parturition, litter size, number of implantation sites, pup survival, sex ratio, lactation index, and onset of sexual maturation in the F1 generation. Ovary weight adjusted for body weight changes was significantly reduced in high-dose females of the F0 and F1 generations; however, ovarian function (as measured by estrus cycle and mating behavior) and histopathology were normal. Testicular and epididymal sperm concentration, motility, and morphology of epididymal sperm, were also unaffected by D79P. The pathological examination

⁵ Initial doses were approximately 71 (0.1%), 358 (0.5%), and 2000 (1.0%) mg/kg/day. Over the course of the study, doses (in mg/kg/day) for male F0 rats ranged from 58-100 (0.1%), 278-530 (0.5%), and 609-2000 (1.0%) from pre-mating through mating. Doses for female F0 rats ranged from 66-165 (0.1%), 340-845 (0.5%), and 693-2000 (1.0%) from pre-mating through the end of lactation. In the F1 generation, male rats were fed doses ranging from 60-166 (0.1%), 298-825 (0.5%), and 648-1705 (1.0%) during the period after weaning and throughout mating. F1 females received 72-165 (0.1%), 363-871 (0.5%), and 747-1800 (1.0%) from when they were weaned, and throughout mating, gestation, and lactation.

of reproductive organs revealed no significant differences from control animals in either sex in the F0 and F1 generations.

High-dose F0 and F1 males had significantly reduced body weights compared with controls. This effect in F0 female rats was less pronounced, and not significant in F1 females. Body weights of offspring of high-dose parents were slightly lower during weaning, although this difference did not last into adulthood. Reductions in organ weights were observed almost exclusively in the high-dose group and, except for liver, could be related to body weight reductions. The affected organs were adrenal glands, spleen, kidney, and thymus in both sexes of the F0 and F1 generations, as well as the ovaries, seminal vesicles, epididymides, and prostate. Liver weight was higher in male and female offspring of rats receiving 1.0% D79P. Initially, male offspring showed a dose-related increase in liver weight; as these animals matured, liver weights decreased in a dose-related fashion, with evidence of severe and regenerative hyperplasia. In mature animals, a number of histopathological changes, including foci development, vacuolation, congestion, hypertrophy, hyperplasia, and necrosis of various cell types were observed in male rats in particular of the F1 and F0 generations. In addition, statistically significant increases in palmitoyl CoA oxidase activity were observed at the 0.5 and 1.0 percent dose levels in F1 animals.

Study authors established a NOAEL of 0.5 percent for reproductive effects based on transient body weight gain reduction in male and female offspring and reduced absolute and adjusted ovary weights at the high dose. The NOAEL for systemic toxicity was not established by study authors because of significantly increased liver weights among F2 male weanlings at all dose levels (Willoughby et al. 2000).

The developmental effects of D79P were evaluated in Sprague-Dawley rats. Female rats (22/dose) were dosed with 0, 250, 500, or 1000 mg/kg/day D79P via gavage between gestation days (GD) 1 and 19, then they were sacrificed on GD 20 (Fulcher et al. 2001). Dams were examined macroscopically for signs of toxicity, and their reproductive tracts were removed to evaluate the gravid uterine weight, number of corpora lutea per ovary, numbers of implantation and resorption sites, and number and distribution of fetuses per uterine horn. There was no sign of maternal toxicity, including body weight changes, throughout the test. In fetuses, the high-dose group had a significantly higher incidence of supernumerary lumbar ribs; no other effects were significant and dose-dependent. The NOAELs for maternal and developmental toxicity were determined to be 1000 mg/kg/day and 500 mg/kg/day, respectively (Fulcher et al. 2001).

Genotoxicity

No studies on the genotoxicity of 1,2-benzenedicarboxylic acid di-C7-C9-phthalate, branched and linear were identified in a search of the relevant literature. In the HPV test plan for the phthalate esters category, a negative Ames assay was reported for this substance, but no reference or further study details were provided (U.S. EPA 2001).

Carcinogenicity

No studies on the carcinogenicity of 1,2-benzenedicarboxylic acid di-C7-C9-phthalate, branched and linear were identified in a search of the relevant literature.

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**Table 21: Summary of Toxicity Data for 1,2-Benzenedicarboxylic Acid, Di-C7-9-Branched and Linear Alkyl Esters
(CAS #68515-41-3)**

Model	Exposure Route	Dose	Dose Duration	Endpoint	Effect	Reference
CFE rats	Gavage	<u>Linevol 7-9 phthalate</u> : 5 mL/kg bw	7 days		Periportal cytoplasmic vacuolation of the liver	Brown et al. 1970
Wistar rats	Gavage	2500 mg/kg bw/day	7 or 21 days		<p>7 days: liver enlargement and liver enzyme changes (M and F); ↓ body wt gain (M), changes in liver structure (M).</p> <p>21 days, M: ↓ growth; ↓ testis wt; bilateral tubular atrophy; liver enlargement, ↓ liver enzyme activities (succinate dehydrogenase, 7-ethoxycoumarin o-deethylase, aniline 4-hydroxylase, glucose-6-phosphatase, alcohol dehydrogenase, microsomal protein content, and cytochrome P-450); hepatocytes changes</p> <p>21 days, F: ↑ body wt gain, enlarged liver, ↓ hepatic cyt P450 and glucose-6-phosphatase activities; ↑ alcohol dehydrogenase activity; hepatocyte changes</p>	Mangham et al. 1981
CFE rats	Dietary	0.125, 0.25, 0.5, or 1.0%	90-day	NOEL = 0.125% (~60 mg/kg/day)	<p><u>0.25%</u>: ↓ hemoglobin levels, ↓ red blood cell counts, and ↑ urinary cell excretion;</p> <p><u>0.5%</u>: ↑ liver and kidney wts; ↓ in hematocrit, hemoglobin, and red</p>	Gaunt et al. 1968

					blood cell counts. <u>1.0%:</u> ↑ liver and kidney wts; ↓ growth rate (M); abnormal urine concentration; ↑ relative brain and gonad wts; ↑ hemosiderin in the spleen (M and F); ↓ in hematocrit, hemoglobin, and red blood cell counts.	
Sprague Dawley rats	Dietary	<p><u>D79P</u> 0, 0.1, 0.5, or 1.0% Equiv. doses (mg/kg/day): <i>Initial</i>- 71; 358; 2000</p> <p><i>Pre-mating throughout mating</i> F0 (M): 58-100; 278-530; 609-2000.</p> <p><i>Pre-mating through end of lactation</i> F0 (F): 66-165; 340-845; 693-2000</p> <p><i>From weaning, throughout mating</i> F1 (M): 60-166; 298-825; 648-1705</p> <p><i>From weaning, through end of</i></p>	<p>F0: 10 wks before mating and throughout the mating, gestation and lactation</p> <p>F1: From weaning and then throughout mating, gestation and lactation.</p>	<p>NOAEL_{reproductive} = 0.5%</p> <p>NOAEL_{systemic} < 0.1%</p>	<p><u>0.1%:</u> ↑ liver wts (F2 M weanlings all doses)</p> <p><u>0.5%:</u> Transient ↓ body wt gain (M/F offspring); ↑ in palmitoyl CoA oxidase activity (F1); ↑ liver wt (F F0/F1/F2)</p> <p><u>1.0%:</u> ↓ gestation length (F0); ↓ body wt on PND 14, 21, 25 (F F1 and F F2 on PND 25 only).</p> <p>↓ Terminal bw (M F0/F1, F F0); ↓ abs wt of adrenal glands, spleen, kidney and thymus (M F0/F1); ↓ abs wt of seminal vesicle, testes (M F1); ↓ abs wt ovaries, adrenal gland, spleen, thymus (F F0/F1), ↓ abs wt kidneys (F F0). ↓ adj wt kidneys epididymides, testes (M F0/F1), and ovaries (F0). Δ liver wt (M/F F0/F1/F2); severe, regenerative liver hyperplasia and histopathological changes (partic. F1 and F0 M)</p>	Willoughby et al. 2000

		<i>lactation</i> F1 (F): 72-165; 363-871; 747- 1800				
Sprague-Dawley rats	Gavage	0, 250, 500, or 1000 mg/kg/day	GD 1-19	NOAEL _{maternal} = 1000 mg/kg/day NOAEL _{developmental} = 500 mg/kg/day	500 mg/kg/day: ↑ incidence of supernumerary lumbar ribs)	Fulcher et al. 2001

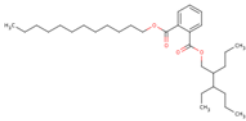
1,2-BENZENEDICARBOXYLIC ACID, DIUNDECYL ESTER, BRANCHED AND LINEAR (CAS #85507-79-5)

1,2-Benzenedicarboxylic acid, diundecyl ester, branched and linear is used as a PVC plasticizer in wire and cable applications, high performance film and sheeting, and low fogging automotive interiors. As a plasticizer, 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear has low volatility and performs well at low temperatures (SpecialChem S.A. 2010).

Specific exposure data for 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear were not found in a search of the literature. Occupational exposure through inhalation of aerosols or dermal contact is possible in settings where this substance is manufactured or where it is used as a plasticizer in the manufacture of another product.

Physicochemical Properties

The physicochemical properties of 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear are summarized below in Table 22.

Table 22: Physicochemical Properties of 1,2,- Benzenedicarboxylic Acid, Diundecyl Ester, Branched and Linear	
Identification	Information
Chemical Name	1,2-Benzenedicarboxylic acid, diundecyl ester, branched and linear
Synonyms	Diundecyl phthalate; 1,2-Benzenedicarboxylic acid, diundecyl ester; Branched and linear diundecyl phthalate; Phthalic acid, diundecyl (C11) ester; Jayflex DIUP; Uniplex DUP
CAS Number	85507-79-5
Structure	 (one structural example)
Chemical Formula	C ₃₀ H ₅₀ O ₄
Molecular Weight	474.7
Physical State	Liquid
Melting Point	-9°C (U.S EPA 2010)
Boiling Point	270° C @ 6.66 hPa
Vapor Pressure	<0.01 hPa @ 20°C
Water Solubility	1.1 mg/L (for diundecyl phthalate; Cousins and MacKay 2000)
Log K _{ow}	10.33 @ 25°C (for diundecyl phthalate; Cousins

	and MacKay 2000)
Flashpoint	> 200°C
Source	ECB 2000 (unless otherwise stated)

Acute Toxicity

The oral LD₅₀ of 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear in rats was determined to be >15,000 mg/kg b.w. In addition, a six-hour inhalation LC₅₀ value of >1.8 mg/L was derived in rats. The dermal LD₅₀ in rabbits was >7900 mg/kg b.w. (ECB 2000).

Irritation and Sensitization

1,2-Benzenedicarboxylic acid, diundecyl ester, branched and linear was classified as not irritating to skin and eyes of rabbits (ECB 2000). No further data on irritation or sensitization were identified for 1,2-benzenedicarboxylic acid, benzyl, diundecyl ester, branched and linear.

Systemic Toxicity

Male and female Fisher 344 rats (10/dose) were fed 0, 0.3, 1.2, or 2.5 percent 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear in the diet for 21 days. The NOAEL was reported to be 0.3 percent (approximately 320 mg/kg bw/day)⁶, although the critical effect was not provided in the available data summary. There was some evidence of peroxisome proliferation at the high-dose level (ECB 2000).

Reproductive and Developmental Toxicity

There were no data identified on the reproductive or developmental toxicity of 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear.

Genotoxicity

Three summaries of unpublished studies on the genotoxicity of 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear indicate that this compound is not mutagenic. In a liquid preincubation protocol reverse mutation assay, *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 were exposed to 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear in the absence or presence of hamster or rat liver S-9 preparation. The test compound was not mutagenic to *S. typhimurium* in the presence or absence of metabolic activation under conditions described here (ECB 2000).

The mutagenicity of 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear was tested in the mouse lymphoma assay under OECD Guideline 476. The test substance did not induce a significant increase in forward mutations in L5178Y mouse lymphoma cells at concentrations of 1.0-10.0 µL/mL with or without metabolic activation. Cytotoxicity was

⁶ Based on male and female default food intakes of 0.100 and 0.113 kg food/kg bw/day, respectively, for Fisher 344 rats (U.S. EPA 1988).

observed at higher (unspecified) concentrations. Under conditions of this assay, 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear was not mutagenic to mouse lymphoma cells (ECB 2000).

In a Balb/c-3T3 mouse cell transformation assay, 4-100 µL/mL 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear was tested in the absence of metabolic activation. A significant increase in cell transformations was observed at one concentration in glass culture vessels only. The dose producing a positive response was not named, nor was the significance of the glass culture vessel. No further details about this assay were provided and the outcome was reported as “negative” in the European Commission’s IUCLID dataset (ECB 2000).

Carcinogenicity

There were no data identified on the carcinogenicity of 1,2-benzenedicarboxylic acid, diundecyl ester, branched and linear.

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1,2-BENZENEDICARBOXYLIC ACID, DI-C11-14-BRANCHED ALKYL ESTERS, C13 RICH (CAS #68515-47-9)

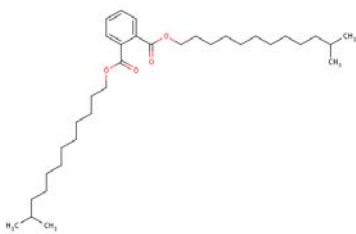
1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich (diisotridecyl phthalate; DITDP) is a high molecular weight phthalate diester mixture comprising branched alkyl chains primarily of 13 carbons, but also of 11, 12, and 14. In Australia, DITDP is used as a component of air compressor lubricants (NICNAS 2008).

Exposure

Exposure to 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich is anticipated in occupational settings where this substance is manufactured or used to produce a consumer product. Exxon Chemicals has proposed an Occupational Exposure Limit (OEL) of 5 mg/m³ for this compound (ECB 2000).

Physicochemical Properties

The physicochemical properties of 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich (CAS #68515-47-9) are summarized below in Table 23.

Table 23: Physicochemical Properties of 1,2-Benzenedicarboxylic Acid, di-C11-14-branched Alkyl Esters, C13 Rich	
Identification	Information
Chemical Name	1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich
Synonyms	Diisotridecyl phthalate; 1,2-bis(11-methyldodecyl) benzene-1,2-dicarboxylate; Emkarate 3020; Jayflex DTDP; Jayflex DTDP-Z; Ergoplast FTD
CAS Number	68515-47-9
Structure	 (one of many components)
Chemical Formula	C ₃₄ H ₅₈ O ₄ (based on C13 length)
Molecular Weight	530.8
Physical State	Liquid
Melting Point	-30°C
Boiling Point	286°C

Vapor Pressure	<0.1 hPa @ 20°C
Water Solubility	<0.1 mg/L volume-% @ 20°C
Log K _{ow}	>5 @23°C
Flashpoint	>200°C
Source	ECB 2000

Toxicokinetics

No data on the toxicokinetics of 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich were identified in a search of the literature.

Acute Toxicity

The acute toxicity of 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich is low in multiple-exposure scenarios. In rats, oral LD₅₀ values >10,000 mg/kg body weight (bw) have been established indicating a low order of toxicity. Dermal LD₅₀ values obtained in rabbits range from >3160 mg/kg bw to >20,000 mg/kg bw (ECB 2000).

Male and female New Zealand albino rabbits (2/sex/dose) with 20 percent shaved body hair were exposed to the Exxon product MRD-81-20⁷ (CAS #68515-47-9) at 50, 200, 794, or 3160 mg/kg bw for 24 hours with an occlusive patch. Exposure was followed by a 14-day observation period. There was no mortality in any dose group, so the dermal LD₅₀ was determined to be greater than 3120 mg/kg bw. A dose-dependent increase in the severity of erythema was noted, reaching a severe level in some animals at the highest dose after 24 hours and 3 days, and then almost disappearing again by day 7 (Exxon Chem. 1982a).

Irritation and Sensitization

As with many other phthalates, the available data suggest that 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich is not expected to be an important dermal or ocular irritant. It was found to be nonirritating to rabbits with a Primary Irritation Index of 0.21 on a scale of 0-8 (NICNAS 2008). Primary skin irritation of the related compound dinitridecyl phthalate (CAS #119-06-2) tested on the belly of albino rabbits rated 2 out of 10, indicating very mild irritation.

Two independent studies showed 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich to be nonirritating to rabbit eyes. Another study indicated that slight, transient conjunctival irritation was produced in the eyes of rabbits. The maximum total Draize score observed was 14 on a scale of 0 to 110. Group mean scores at 24, 48, and 72 hours were 1.0, 0.33, and 0 for conjunctival redness and 0.67, 0, and 0 for chemosis. No iridial or corneal effects were noted (NICNAS 2008). In another study, a 24-hour exposure to dinitridecyl phthalate produced corneal injury in rabbits that rated 2 on a scale of 10 (Smyth et al. 1962).

⁷ This is the same test product and test report as another Exxon report (EPA/OTS Doc #878210432); only the CAS # is different. See Acute Toxicity section under CAS #68515-41-3 in this report.

In the Buehler test, 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich was reported to be nonsensitizing under OECD Guideline 406. None of 20 guinea pigs showed dermal sensitization from induction and challenge with 100 percent test substance (ECB 2000). Diisotridecyl phthalate was tested for dermal irritation and sensitization among 104 people. No irritation was noted after a 24-hour occluded patch exposure of undiluted diisotridecyl phthalate to human skin. There was also no evidence for dermal sensitization in the human repeated insult patch test (HRIPT) using the modified Draize p ion potential (Medeiros et al. 1999).

Systemic Toxicity

No data on the systemic toxicity of 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich were identified in a search of the literature.

Ditridecyl phthalate (CAS # 119-06-2), along with six other phthalate compounds, were evaluated for cell proliferation potency using the human mammary carcinoma cell line (MCF-7). Ditridecyl phthalate's proliferative effect relative to estradiol was insignificant at 67 percent. None of the phthalates demonstrated significant relative proliferative potency compared to estradiol. The competitive inhibition of the same six phthalate compounds versus estradiol was also evaluated in this study. Ditridecyl phthalate was considered inactive with respect to relative binding affinity (RBA) for the human estrogen receptor (Kim and Ryu 2006).

Doses of estradiol (0.3, 3, or 30 µg/kg) or ditridecyl phthalate (20, 200, or 2000 mg/kg b.w.) were administered to Sprague-Dawley rats subcutaneously in an *in vivo* uterotrophic assay. Estradiol significantly increased uterine wet weights at each dose level, while ditridecyl phthalate did not at any dose, thereby confirming an absence of estrogenicity (Kim and Ryu 2006).

Reproductive and Developmental Toxicity

No data on the reproductive or developmental toxicity of 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich were identified in a search of the literature.

Genotoxicity

In a reverse mutation (Ames) assay, *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to doses of 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich as high as 5000 µg/plate. The test compound was not mutagenic in the presence or absence of metabolic activation (ECB 2000). Likewise, Zeiger et al. (1985) determined the test substance was not mutagenic to *S. typhimurium* strain TA100 in the presence or absence of S-9 at doses up to 10 mg/plate.

Carcinogenicity

No data on the carcinogenicity of 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich were identified in a search of the literature.

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1,2-BENZENEDICARBOXYLIC ACID, 1-(2,2-DIMETHYL-1-(1-METHYLETHYL)-3-(2-METHYL-1-OXOPROPOXY)PROPYL) 2-(PHENYLMETHYL) ESTER (CAS #16883-83-3)

1,2-Benzenedicarboxylic acid, 1-(2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl) 2-(phenylmethyl) ester (DMMEMOPPPM), often called by its trade name Texanol benzyl phthalate, is derived from 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate (CAS #25265-77-4), benzyl alcohol, and phthalic acid. In 1998, Texanol benzyl phthalate was listed on the U.S. EPA's HPV Chemicals list with an annual domestic production of 6.73 to 8.90 million pounds (Tice 1999). The estimated U.S.-manufactured plus imported volume of DMMEMOPPPM between 1985 and 2005, was 1 million to 10 million pounds per year (U.S. EPA 2002; U.S. EPA 2006a).

Texanol benzyl phthalate is used as a plasticizer in vinyl systems to which it imparts migration resistance, durability, adhesion, and resistance to water spotting. Specific applications using Texanol benzyl phthalate-based plasticizers include paints, coatings, automotive sealants, and in caulks and sealants that are based on chlorinated rubber, butyl rubber, polysulfides, water-blown methylene diisocyanate (MDI)-based polyurethane foams, poly(vinyl chloride)-containing conductive fillers, and electromagnetic shields. It is also used as a yellowing inhibitor for thermoplastic polycarbonate resins exposed to gamma radiation, as a fade-resistance solvent for pressure-sensitive copying paper and for interlayers of sandwich glass for cars and buildings (Tice 1999).

Exposure

The most likely routes of exposure to this compound are dermal contact and inhalation (Tice 1999). Monsanto recommended a time-weighted average exposure limit of 5 mg/m³ for Texanol benzyl phthalate, although the derivation of this exposure limit is not known (Tice 1999).

Physicochemical Properties

The physicochemical properties of 1,2-benzenedicarboxylic acid, 1-(2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl) 2-(phenylmethyl) ester are listed below in Table 24.

Table 24: Physicochemical Properties of 1,2-benzenedicarboxylic acid, 1-(2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl) 2-(phenylmethyl) ester

Identification	Information
Chemical Name	1,2-Benzenedicarboxylic acid, 1-(2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl) 2-(phenylmethyl) ester
Synonyms	Benzyl 2,2-dimethyl-1-isopropyl-3-(2-methyl-1-oxopropoxy)propyl phthalate; 1,2-Benzenedicarboxylic acid, 2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl phenylmethyl ester; Benzyl 3-isobutyryloxy-1-isopropyl-2,2-dimethylpropyl phthalate; 1,2-Benzenedicarboxylic acid, 2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl phenylmethyl 1,2-benzenedicarboxylate; Isobutyric acid, 3-hydroxy-2,2,4-trimethylpentyl ester benzyl phthalate; 1,3-Pentanediol, 2,2,4-trimethyl-, 3-(benzyl phthalate) isobutyrate; Phthalic acid, benzyl 3-hydroxy-1-isopropyl-2,2-dimethylpropyl ester isobutyrate; 2,2,4-Trimethyl-1,3-pentanediol 1-isobutyrate benzyl phthalate; Santicizer® 278 (Monsanto); Texanol benzyl phthalate (Monsanto).
CAS Number	16883-83-3
Structure	
Chemical Formula	C ₂₇ H ₃₄ O ₆
Molecular Weight	454.6
Physical State	Liquid
Color	Clear
Boiling Point	243°C (13.33 hPa)
Vapor Pressure	0.66 hPa
Water Solubility	0.81 mg/L (22°C)
Log K _{ow}	>6 (20°C)
Flashpoint	227°C
Source	U.S. EPA 2006b, Tice 1999

Acute Toxicity

An oral LD₅₀ of >15,800 mg/kg bw was established in rats for the compound 1,2-benzenedicarboxylic acid, 1-(2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl) 2-(phenylmethyl) ester (DMMEMOPPPM). Acute effects included reduced appetite and temporary slight weakness. A dermal LD₅₀ of >10,000 mg/kg bw was established using one male and one female rabbit (U.S. EPA 2006b).

Irritation and Sensitization

DMMEMOPPPM was not irritating to skin in a 24-hour exposure using one male and two female rabbits. Ocular effects were classified as “not irritating” to “slightly irritating” in rabbits (U.S. EPA 2006b).

Monsanto, the original producers of Texanol benzyl phthalate, reported that the compound does not cause significant eye or skin irritation in humans (reported in Tice 1999) or toxicity, nor significant inhalation or ingestion toxicity.

Systemic Toxicity

There were no data identified on the systemic toxicity of DMMEMOPPPM. Monsanto, the original producers of Texanol benzyl phthalate, reported that the compound does not cause significant toxicity following inhalation or ingestion in humans (reported in Tice 1999).

Reproductive and Developmental Toxicity

There were no data identified on the reproductive or developmental toxicity of DMMEMOPPPM.

Genotoxicity

In the Ames assay, *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to 0.01, 0.04, 0.2, 1.0, 3.0, or 10 mg/plate of DMMEMOPPPM. The test compound was not mutagenic in the presence or absence of metabolic activation (U.S. EPA 2006b).

Carcinogenicity

There were no data identified on the carcinogenicity of DMMEMOPPPM.

References

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1,2,-BENZENEDICARBOXYLIC ACID, BENZYL, C7-9 BRANCHED AND LINEAR ALKYL ESTERS (CAS #68515-40-2)



1,2-Benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters, a component of Santicizer® 261 Plasticizer, is used in polyurethane and polysulfide caulks and sealants, film and sheeting, flooring, coated fabrics, plastisols, organosols, vinyl foams, acrylic lacquers, calendering, extrusions, slush molding, inks, adhesives, elastomers, wire, and cable (Ferro 2010; Ash and Ash 2004).

Exposure

Exposure to 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters is anticipated in occupational settings where this substance is manufactured or used to produce a consumer product. The OSHA-permissible exposure limit (PEL) for 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters is 5.0 mg/m³ (Epoxy Systems 2008).

Physicochemical Properties

The physicochemical properties of 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters are summarized below in Table 25.

Table 25: Physicochemical Properties of 1,2,-Benzenedicarboxylic Acid, Benzyl, C7-9 branched and linear alkyl esters	
Identification	Information
Chemical Name	1,2,-Benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters
Synonyms	Benzyl C7-9-branched and linear alkyl phthalates; Phthalic acid, benzyl alkyl(C7-C9) ester;
CAS Number	68515-40-2
Structure	 R =  R' = C ₇ H ₁₅ or C ₉ H ₁₉ (branched or linear)
Chemical Formula	C ₂₁ H ₂₅ O ₄ (based on C7 length)
Molecular Weight	341.4 – 369.5
Physical State	Liquid
Color	Clear
Boiling Point	252-390°C
Vapor Pressure	0.667 hPa @ 200°C
Water Solubility	0.3 mg/L @25°C
Log K _{ow}	5.5 @20°C
Flashpoint	229 °C
Source	ECB 2000

Toxicokinetics

There were no data identified on the toxicokinetics of 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters.

Acute toxicity

The acute toxicity of 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters is low in multiple exposure scenarios. In a limited study in rats, an oral LD₅₀ value >15,800 mg/kg body weight (bw) was established indicating a low order of toxicity. A dermal LD₅₀ of >7940 mg/kg bw was derived in rabbits, who showed decreased appetite and activity (ECB 2000).

Santicizer® 261 is a mixture comprising benzyl chloride, C7 alcohols, C9 alcohols, benzal chloride, toluene, and 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters in an unknown ratio (Monsanto 1975). An oral LD₅₀ value of 1580 mg/kg bw was determined for Santicizer® 261 in male Sprague-Dawley albino rats. All rats (5/5) died at the highest dose tested, 5000 mg/kg bw. Outward signs of toxicity included reduced appetite and activity and weakness. An autopsy of the dead rats revealed hemorrhagic lungs and liver and acute gastrointestinal inflammation. The dermal LD₅₀ for Santicizer® 261 was determined to be >2000 mg/kg bw in New Zealand albino rabbits. Manifestations of toxicity were similar to the acute oral dose, and also included slight liver discoloration and enlarged gall bladder (Monsanto 1975).

Irritation and Sensitization

After a 24-hour exposure to intact or abraded skin in rabbits, 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters was classified as slightly irritating by the Younger Laboratory Method, and not irritating based on the European Commission classification (ECB 2000). In a primary dermal irritation test, undiluted Santicizer® 261 was tested in New Zealand albino rabbits for 24 hours. Santicizer® 261 was classified as a severe dermal irritant; observations included defatting and skin sloughing after 10–14 days (Monsanto 1975).

In a Draize test, rabbits exposed via the eye to 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters showed slight ocular irritation, as defined by the Draize assay, and no irritation, as defined by the European Commission (ECB 2000). Monsanto (1975) tested the acute eye irritation of undiluted Santicizer® 261 in New Zealand albino rabbits with a 24-hour exposure. In the first 24 hours, irritation was high in the conjunctivae and cornea. Over time, irritation decreased and reached nil after 168 hours. Overall classification of irritation was “slight.”

No sensitization data were identified for 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters.

Systemic Toxicity

There were no data identified on the systemic toxicity of 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters.

Reproductive and Developmental Toxicity

There were no data identified on the reproductive or developmental toxicity of 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters.

Genetic Toxicity

In the Ames assay, *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to concentrations of 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters ranging from 0-10 µL/plate. The test compound was not mutagenic in the presence or absence of metabolic activation (ECB 2000).

Carcinogenicity

No studies on the carcinogenicity of 1,2-benzenedicarboxylic acid, benzyl, C7-9 branched and linear alkyl esters were identified in a search of the relevant literature.

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