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Overview of Phthalate Ester Pharmacokinetics in Mammalian Species

by William M. Kluwe*

Phthalic acid esters, or phthalate esters, are generally well absorbed from the gastrointestinal tract following oral administration. Hydrolysis to the corresponding monoester metabolite, with release of an alcoholic substituent, largely occurs prior to intestinal absorption of the longer-chain alkyl derivatives such as di(2-ethylhexyl) phthalate (DEHP). Phthalate esters are widely distributed in the body, with the liver being the major, initial repository organ. Clearance from the body is rapid and there is only a slight cumulative potential. Short-chain dialkyl phthalates, such as dimethyl phthalate, can be excreted in an unchanged form or following complete hydrolysis to phthalic acid. Longer-chain compounds such as DEHP, however, are converted principally to polar derivatives of the monoesters by oxidative metabolism prior to excretion. A marked species difference in DEHP metabolism exists: primates (man, monkey, some rodent species) glucuronidate DEHP at the carboxylate moiety following hydrolysis of a single ester linkage, whereas rats appear to be unable to glucuronidate the monoester metabolite and oxidize the residual alkyl chain instead to various ketone and carboxylate derivatives. The major route of phthalate ester elimination from the body is urinary excretion. Certain phthalate esters are excreted in the bile but undergo enterohepatic circulation.

The relationships of phthalate ester pharmacokinetics to their toxicological actions are unknown at the present time, largely due to a lack of elucidated mechanisms of toxic action.

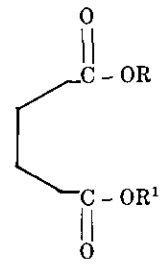
Introduction

It is the intent of this paper to furnish readers with a general background in phthalate ester pharmacokinetics, with emphasis on absorption, distribution, metabolism and excretion in several mammalian species. Subsequent papers in these proceedings address the absorption and metabolism of specific phthalates in more detail than is contained herein. The greatest amount of data, by far, has been collected on di(2-ethylhexyl) phthalate (DEHP), the most commonly used of the poly(vinyl chloride) (PVC) plasticizers. There seem to be sufficient similarities in some pharmacokinetic parameters of the compounds studied to date, however, to permit inferences to be drawn of the pharmacokinetics of dialkyl phthalate esters in general. Attempts to correlate similarities in pharmacokinetics to a generic pattern of toxicity for dialkyl phthalates await elucidation of probable mechanisms of toxic action.

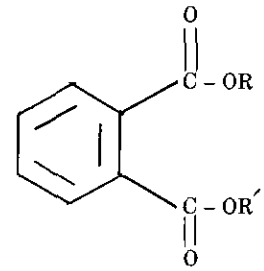
*National Toxicology Program, NIEHS, P.O. Box 12233, Research Triangle Park, North Carolina 27709.

Chemical Structures and Properties

Structurally, phthalate esters consist of paired ester groups on a cyclohexatriene ring (benzenedicarboxylic acid) (Table 1). The *meta* and *para* configurations are known as isophthalates and terephthalates, respectively. The *ortho* configuration, however, is implied in the generic use of the term, "phthalate esters." Phthalate esters are synthesized commercially by condensation of appropriate alcohols with phthalic anhydride as indicated in Table 1. The structures of the ester substituents and the corresponding chemical names of many of

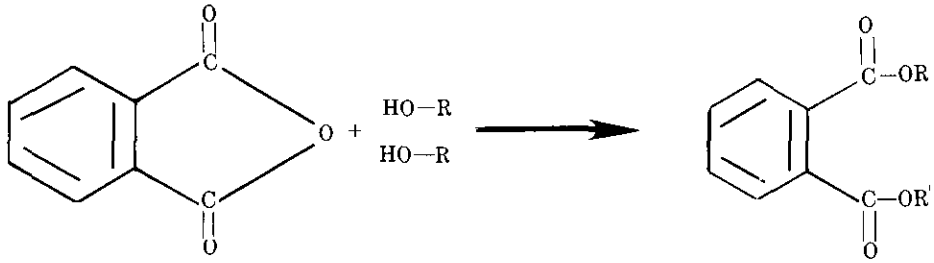


Adipate Esters



Phthalate Esters

Table 1. Structures of several common phthalate esters.



R	R'	Compound
– H	– H	Phthalic acid
– CH_3	– CH_3	Dimethyl phthalate
– $CH_2CH(CH_2)_3CH_3$ $CH_2\ CH_3$	– $CH_2CH(CH_2)_3CH_3$ $CH_2\ CH_3$	Di(2-ethylhexyl) phthalate
– $CH_2CH_2OCH_3$	– $CH_2CH_2OCH_3$	Di(2-methoxyethyl) phthalate
– $(CH_2)_3CH_3$	– $CH_2C_6H_5$	Butyl benzyl phthalate
– $(CH_2)_3CH_3$	– $CH_2COO(CH_2)_3CH_3$	Butylglycolyl butyl phthalate (Butyl phthalylbutyl glycolate)

the more widely used phthalate esters are also shown. In the related plasticizers, the adipate esters, a four-carbon chain separates the two ester groups.

Specific phthalate esters with short alkyl groups, such as dimethyl and di-*n*-butyl phthalates, are appreciably soluble (e.g., 0.5 g/100 ml) in water (*1*). Most other dialkyl phthalates, however, including DEHP, are relatively insoluble in aqueous mediums because of their lipophilic structures. Volatilities at standard temperature and pressure are generally low, particularly for the long-chain and branched compounds, such as DEHP.

Absorption

Dermal and pulmonary tissues would not be predicted to be major barriers to absorption of phthalate esters from the skin or lungs because of the lipophilic nature of the chemicals. Quantitative (and in most cases qualitative) data on absorption by these routes, however, are nonexistent or unavailable at the present time. Phthalate esters, principally DEHP, can also be introduced directly into the circulatory system by the use of plasticized PVC medical equipment (e.g., syringes or tubing) or by infusions from plasticized PVC blood bags. For other than occupationally or medically exposed populations, however, the most common mode of human contact with phthalate esters is ingestion with food or liquids.

The extent of intestinal absorption of phthalate esters has been estimated by monitoring urinary excretion of the compounds or their metabolites after administering a known amount of compound orally. Shown in Table 2 are the approximate percentages of the ingested dose extracted from the urine of rats given one of several phthalate esters. Absorption of phthalic acid itself appears to be incomplete, but in excess of 90% of oral doses of di-*n*-butyl phthalate over a range of 60 mg/kg to 2.31 g/kg was excreted in the urine within 2 days, indicating complete or near-complete intestinal absorption of this compound. Lesser percentages (~ 40–50%) of DEHP given by gavage in doses of 3 mg/kg or 1.0 g/kg appeared in urine, but greater than 90% of concentrations of 10 or 2000 ppm incorporated in feed were excreted by this route (Table 2). Thus, DEHP in food appears to be very well absorbed from the intestine over a very wide concentration range. The data in Table 2 also indicate that di(3,5-dimethoxyethyl) phthalate, butyl phthalylbutyl glycolate and the DEHP hydrolysis product, mono(2-ethylhexyl) phthalate (MEHP) are all well absorbed from the intestine. Based on this information, it can be speculated that dialkyl phthalate esters, in general, are well absorbed following oral ingestion. In contrast, little is known of the absorptive characteristics of phthalate esters with aromatic alcohol substituents.

Both ester linkages of phthalate esters can be hydrolyzed, leaving phthalic acid as a product. Hydrolysis of a single ester group, however, occurs much more readily than hydrolysis of the second. Esterases capable of generating the monoester metabolite are present in several mammalian tissues (*9*), including intestinal mucosal cells (*10*). Extracellular enzymes present in the intestinal contents are also capable of hydrolyzing DEHP and other phthalate esters (*10, 11*). As shown in Table 3, short-alkyl-chain congeners are more readily metabolized by intestinal contents than are long-alkyl-chain congeners; the extent of completeness of the reaction is also inversely proportional to the concentrations of the diester compounds.

The hydrolytic activity of the intestinal contents

Table 2. Estimation of intestinal absorption of phthalate esters in rats.

Compound[a]	Dose[b]	Time[c]	Percentage of dose excreted in urine	Reference
PA	40 mg/kg	4 days	25	(2)
DBP	60 mg/kg	48 hr	90	(3)
	270 mg/kg	48 hr	90	(4)
	2.31 g/kg	48 hr	90	(5)
DEHP	3 mg/kg	4 days	40	(6)
	1 g/kg	24 hr	50	(4)
	10 ppm[d]	—[e]	> 90	(4)
	2000 ppm[d]	—[e]	> 90	(4)
MEHP	50 mg/kg	24 hr	70	(7)
DiOP	50 mg/kg	4 days	60	(8)
BPBG	50 mg/kg	4 days	80	(8)

[a]PA, phthalic acid; DBP, di-*n*-butyl phthalate; DEHP, di(2-ethylhexyl) phthalate; MEHP, mono (2-ethylhexyl) phthalate; DiOP, di(3,5-dimethylhexyl) phthalate; BPBG, butyl phthalylbutyl glycolate.
[b]Oral gavage, unless specified otherwise.
[c]Period of sample collection, between exposure and termination.
[d]Concentration incorporated into feed.
[e]Time not reported.

Table 3. Hydrolysis of phthalate esters by rat intestinal contents.[a]

Compound[b]	Concentration, mg/ml	Portion metabolized, %[c]	Reference
DMP	1	60	(11)
DBP	1	80	
DEHP	1	20	
DOP	1	10	
DEHP	0.1	100	(10)

[a]The chemicals were incubated for 16 hr at 37°C under an N_2 atmosphere in 20% (*v/v*) suspensions of gut contents in phosphate-buffered Ringers solution containing 1% (*w/v*) D-glucose.
[b]DMP, dimethyl phthalate; DBP, di-*n*-butyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DOP, di-*n*-octyl phthalate.
[c]Percent metabolized in 16 hr.

towards phthalate esters *in vitro* is heat (boiling) labile, but unaffected by either filtration of cellular material or by bacteriocidal sterilization of the gut (*10, 11*). Hence, the hydrolytic activity appears to be enzymic in nature, though not of bacterial origin. Albro and Thomas (*12*) have reported very high hydrolytic activity towards DEHP in pancreatic homogenates, implicating the intestinal secretion of pancreatic enzymes as a source of gut hydrolytic activity towards phthalate esters, and predicting that little or no intact diester compound is absorbed from the intestine. The latter hypothesis, that primarily MEHP is absorbed after oral administration of DEHP, raises the question of whether oral and intravenous (and, possibly, inhalation and dermal) routes of DEHP administration represent similar or dissimilar types of exposure.

Distribution

Some of the earlier studies on phthalate ester distributions in the body, particularly those using the intravenous route, were complicated by poor aqueous solubility of the chemicals and artifacts later attributed to phthalate-solubilizer interactions. More recent studies have utilized plasma-solubilized compounds. Virtually all DEHP in blood is protein-bound, approximately 80% to lipoproteins and the rest to albumin (*13*). MEHP in blood, ostensibly a product of DEHP hydrolysis by blood esterases (*14*), equilibrates between free and albumin-bound forms (*13*).

Whether administered by oral or parenteral routes, DEHP and di-*n*-butyl phthalate (DBP), the two compounds studied most extensively, are rapidly cleared from the body (*3-6, 15*). The bulk of the chemicals is cleared within 24 hr and nearly none is left 3-5 days after exposure; there is little or no evidence of tissue accumulation or prolonged tissue retention. The pharmacokinetic behavior of MEHP is similar to that of DEHP (*7*). Fat, absorptive organs (gastrointestinal tract) and excretory organs (liver, kidney, gastrointestinal tract) are the major initial repositories for the dialkyl esters (Table 4). MEHP is not readily deposited in adipose tissue (Table 4), suggesting that perhaps unmetabolized dialkyl compounds, rather than their monoester metabolites, partition most readily into fat. Liver, kidney and gastrointestinal tract probably accumulate the phthalate esters as a mechanism of excre-

Table 4. Distribution of orally administered phthalate esters.

Compound[a]	Species	Dose, mg/kg	Time[b]	Repository organs	Reference
DBP	Rat	60	24 hr	Intestine, adipose, liver, kidney, muscle	(*3*)
	Rat	270	24 hr	Liver, kidney, adipose	(*5*)
			48 hr	None	
DEHP	Rat	500	24 hr	Intestine, stomach, liver, kidney, adipose	(*15*)
	Rat	800	24 hr	Liver, kidney, adipose, muscle, testis	(*4*)
			4 days	Adipose	
DiOP	Rat, dog, pig	50	4 hr	GI, adipose, liver, muscle	(*8*)
			24 hr	GI, adipose	
			4 days	None	
MEHP	Rat	69	24 hr	Intestine, heart, liver, kidney, lungs, muscle	(*7*)
BPBG	Rat, dog, pig	50	4 hr	GI, liver, muscle, adipose	(*8*)
			24 hr	GI	
			4 days	None	

[a]DBP, di-*n*-butyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DiOP, di(3,5-dimethylhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate, BPBG, butyl phthalylbutyl glycolate.
[b]Time between administration and examination.

Table 5. Steady-state concentration of DEHP in rat liver and abdominal fat upon prolonged dietary ingestion.[a]

	Dietary concn = 1000 ppm		Dietary concn = 5000 ppm	
Time, weeks	Liver	Fat	Liver	Fat
On diet				
1	50 ppm	4 ppm	120 ppm	25 ppm
2	40 ppm	8 ppm	165 ppm	60 ppm
3	46 ppm	7 ppm	—[b]	—
4	46 ppm	9 ppm	110 ppm	60 ppm
5	36 ppm	8 ppm	115 ppm	80 ppm
Off diet				
1	2 ppm	4 ppm	20 ppm	35 ppm
3	none	3 ppm	none	20 ppm

[a]Data derived from Daniel and Bratt (*6*) with the permission of the authors and Elsevier/North Holland. Calculated from radioactivity recovered in the tissues after dietary administration of ^{14}C-DEHP.
[b]Not determined.

tion (e.g., urine, bile) and may, therefore, be inappropriately labeled as repositories.

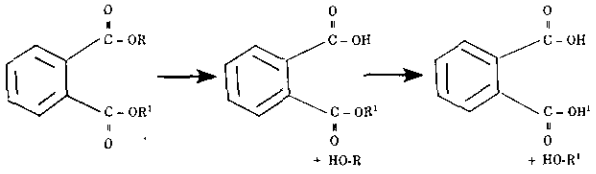
Daniel and Bratt (*6*) examined tissue accumulation of DEHP in rats by monitoring radioactivity in fat and liver after dietary exposure to ^{14}C-DEHP. A synopsis of their results is contained in Table 5. Steady-state concentrations in liver were achieved within a week of initiation of treatment, while that in fat required 2 weeks. The organ difference in time to achieve a steady-state level was mirrored by a difference in the rate of decline after removal of DEHP from the diet: radioactivity in the liver was reduced by 80% in 1 week, and was below detection limits within 3 weeks, while radioactivity in fat was reduced only to approximately one-third of the steady-state level within 3 weeks (Table 5). The steady-state tissue concentrations of radioactivity were proportional to the concentration of DEHP in the diet, indicating that saturation of tissue accumulation had not occurred at up to 1000 ppm in the diet. In contrast to high-dose, oral studies in rats, significant fractions of the cumulative dose of DEHP were reported to be retained for several months in the livers of rhesus monkeys infused (intravenously) repeatedly with very small amounts (cumulative doses of 21–69 mg/kg) of DEHP in blood (*16*).

Surprisingly little is known of the abilities of phthalate esters to be transferred to offspring. Radioactivity was recovered from fetal tissues following treatment of the maternal animals with ^{14}C-DEHP or ^{14}C-diethyl phthalate (*17*). The concentrations in the fetal tissues did not exceed those in the maternal tissues. Maternal-fetal transfer of dialkyl phthalate esters across the placenta, therefore, is likely. Excretion into maternal milk is also a distinct probability since lipophilic chemicals readily partition into high fat materials such as breast milk.

Metabolism

Dialkyl phthalates are metabolized to the monoester products by enzymes present in many tissues, but

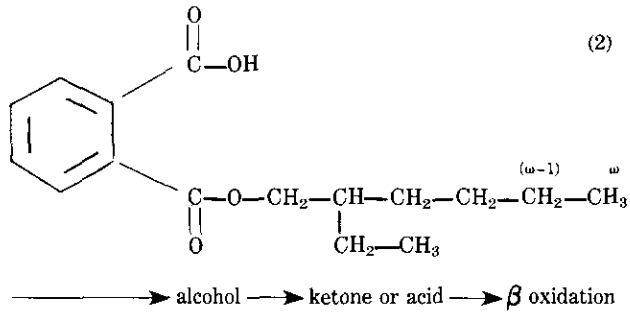
only those in liver are capable of hydrolyzing DEHP completely to phthalic acid (*12*), as shown in Eq. (1). Appreciable amounts of dimethyl phthalate are excreted as phthalic acid, while only very small fractions of DEHP and other long-chain alkyl phthalates are converted to this product (*18, 19*).



(1)

Dimethyl phthalate and, to a lesser extent, DBP can be excreted in urine as the parent, unchanged compounds or as their monoester metabolites (*18*). Phthalate esters with longer chain lengths, however, such as DEHP, must undergo further modification after hydrolysis to the monoester to achieve sufficient polarity for renal excretion. The data in Table 6 indicate that several species of animals form glucuronide conjugates with the monoester metabolite of DBP at the free carboxylate group. The ferret, African Green monkey and man form glucuronide conjugates of MEHP, as well, but rats appear to be unable to do so (Table 6). Recent evidence indicates that hamsters, guinea pigs and mice also excrete glucuronide conjugates of MEHP (*20*). The reason for the inability of rats to conjugate MEHP is unknown. In addition to glucuronidation, the residual alkyl chain is oxidized prior to urinary excretion of the metabolites (*3, 21-26*).

The inability of the rat to metabolize DEHP synthetically requires extensive oxidation of the remaining 2-ethylhexyl moiety to achieve water solubility. A schematic of the metabolism of DEHP in rats, as deduced by Albro et al. (*19*), is shown in Eq. (2). The same general pathways have been documented for metabolism of the monoester derivatives of other dialkyl phthalate esters (*2–7, 18*).



(2)

Following initial oxidation of the terminal (ω) or adjacent (ω – 1) carbon atom in the side chain to an alcohol, aldehydes, ketones and carboxylic acids are formed via successive oxidations. Compounds with long (six or more linear carbons) alkyl chains may undergo β-oxidation and the loss of two-carbon fragments (*18, 19*). Generally, the metabolism of phthalate esters is qualitatively unaffected by the route of administration (*6, 7, 15, 18, 19*).

Excretion

The major route of phthalate ester elimination in both rodent and primate species, including man, is urinary excretion (Table 7) (*23, 24*). Fecal elimination as a route of excretion has been evaluated for only a limited number of phthalate esters (Table 7). Elimination of di-*n*-butyl phthalate (DBP) in feces is nearly nil over a wide dose range. Appreciable percentages of DEHP appeared in feces when the compound was given by gavage, but whether the fecal material represented unabsorbed DEHP or biliary-excreted material was not ascertained (Table 7). Similarly, only 4 and 9% of dietary DEHP at concentrations of 10 and 2000 ppm, respectively, were recovered from the feces of rats, but it is not known whether these materials were bile-excreted or unabsorbed chemical.

Tanaka et al. (*3*) demonstrated biliary excretion of DBP to the extent of 44% in 24 hr after an oral dose of 60 mg/kg. Only 5% of this same dose was

Table 6. Synthetic metabolism of phthalate esters.

Compound	Species	Route	Dose	Conjugated metabolites	Reference
DEHP	Rat	PO	500 mg/kg	MBP-glucuronide	(*21*)
	Rat	PO	60 mg/kg	MBP-glucuronide derivatives	(*3*)
	Guinea pig	—[a]	—[a]	MBP-glucuronide derivatives	(*3*)
	Hamster	—[a]	—[a]	MBP-glucuronide derivatives	(*3*)
DBP	Rat	Various	Various	None	(*4,6,7,15,18,19*)
	Ferret	PO	600 mg/kg	MEHP glucuronide derivatives	(*22*)
	Monkey	IV	—[a]	MEHP glucuronide derivatives	(*23*)
	Human	IV	94-171 mg	MEHP glucuronide derivatives	(*24*)

[a]Not reported.

Table 7. Biliary, fecal and urinary excretion of DBP or DEHP in rats.

Compound	Dose	Time[a]	Route	Portion of dose, %[b]			Reference
				Bile	Feces	Urine	
DBP	60 mg/kg	24 hr	PO	44	5	88	(3)
	500 mg/kg	6 hr	PO	5	—[c]	—	(21)
	2.31 g/kg	48 hr	PO	—	5	82	(5)
	50 mg/kg	5 hr	IV	10	—	—	(21)
DEHP	2.6 mg/kg	4 days	PO	14	56	42	(6)
	1.0 g/kg	4 days	PO	—	40 (8)	60	(5)
	10 ppm	—[c]	Feed	—	4 (0)	96	(4)
	2000 ppm	—	Feed	—	9 (6)	91	(4)
	50 mg/kg	7 days	IV	—	28	49	(15)

[a]Time of collection post treatment.
[b]Metabolites in parentheses.
[c]Not reported.

eliminated in the feces (88% in urine) of nonbile duct cannulated rats (Table 7), indicating extensive enterohepatic cycling. As only 5% of a much larger dose of DBP, 500 mg/kg, was recovered from bile in 6 hr (Table 7), hepato-biliary excretion of DBP metabolites would appear either to be saturated at high doses or to occur only after a specific period of time post absorption. The latter possibility, delayed biliary excretion, is suggested by the finding that only 10% of an intravenous dose of 50 mg/kg DBP was recovered in bile in 5 hr, in comparison to 44% of an oral dose of 60 mg/kg in 24 hr (Table 7). Biliary metabolites of DBP include monobutyl phthalate, monobutyl phthalate glucuronide and oxidized derivatives of monobutyl phthalate glucuronide (*3*, *5*, *21*).

DEHP can also undergo biliary excretion, as indicated by the report of Daniel and Bratt (*6*) that 14% of an oral dose of 2.6 mg/kg was recovered from bile. Extraction of 28% of an intravenous dose of 50 mg/kg DEHP from feces further indicates that biliary excretion can be a significant route of phthalate ester elimination (Table 7). The biliary metabolites of DEHP in rats were characterized as MEHP derivatives; none were glucuronide conjugates (*6*). Although other studies did not specifically collect bile, an estimate of biliary excretion was obtained by separating fecally eliminated material into parent compound (presumably unabsorbed) and metabolites (presumably bile-excreted products). As only 8% of an oral gavage dose of 1.0 g/kg DEHP was isolated from feces as DEHP metabolites (Table 7), either biliary excretion is not a major route of elimination in this dose range or, more likely, the biliary products are reabsorbed from the intestine and excreted in urine. Similar findings occurred in studies where DEHP was administered with food at concentrations of 10 or 2000 ppm (Table 7). Hence, DEHP metabolites appear to be excreted in bile to an unknown extent, reabsorbed from the intestine, and ultimately eliminated in the urine.

Relationships of Phthalate Ester Pharmacokinetics to Toxic Effects

Speculation on possible relationships between comparative pharmacokinetics and toxicities are tenuous, at best, in the absence of well-defined mechanisms of action. The generally rapid clearance and low potential for tissue accumulation of the dialkyl phthalate esters, however, is at least consistent with, if not the cause of, their low toxic potencies in both acute and chronic studies (*25-27*). The primate/rat difference in ability to form glucuronide conjugates of MEHP is suggestive of a major species difference in chemical metabolism. Whether or not such a difference renders the rat an unsuitable model of human response to DEHP exposure awaits elucidation of the mechanisms of DEHP toxicity in rats. However, other species that differ from rats in their ability to glucuronidate MEHP (e.g., mice) respond with the same types of toxic injury as do rats (*25*), indicating possible independence of chemical toxicity from the ability of the experimental subjects to form glucuronide metabolites. Yet to be determined are the precise mechanisms among several species of oxidation of the residual alkyl group and whether or not potential differences in the nature of the oxidation reaction (e.g., NADH-consuming or NADH-producing) could affect the toxic response. In light of the recent report that DEHP is a hepatocarcinogen in rats and mice (*25*), these species differences or potential differences in DEHP metabolism provide a strong stimulus for studying the mechanisms of mammalian response to phthalate ester exposures.

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