Absorption, Metabolism, and Excretion of Di(2-ethylhexyl) Phthalate by Rats and Mice

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There is convincing evidence in the literature that most of the adverse biological effects of phthalate diesters are actually effects of metabolites rather than of the parent compounds. If so, the dramatic species differences in endpoint metabolic profiles make it essential that metabolism of phthalates be understood in detail, including the factors that may alter the metabolism. A metabolic pathway for phthalates having saturated alkyl groups has been postulated based on identification of metabolites produced *in vivo* and excreted in urine. The first few steps in the postulated pathway have been confirmed *in vitro* using enzymatically active preparations from rats and mice; some details of the nature of these early steps have been learned. Although some information concerning later steps is available, much remains to be learned in this area. Species differences are postulated to involve kinetics of several biochemical and physiological events acting in concert or competition. Among these interacting factors are competition of at least three enzymes for phthalate monoesters as substrate, relative kidney clearance rates for different metabolites, relative K_m values of oxidative enzymes for the same precursors in different species, and relative equilibria between glucuronide formation and hydrolysis.

Essential information that must be obtained in the future includes (a) which metabolites play a causal role in which biological effects, and (b) what factors (age, diet, state of health, etc.) can modify the metabolism of phthalate esters and in what way.

Introduction

Presently available evidence strongly suggests that the undesirable biological effects of phthalate esters are mediated by metabolites rather than by the parent compounds *in vivo*. Such effects as testicular atrophy (1) and peroxisome proliferation in rodents (2) are also seen on administration of the primary hydrolysis products of phthalate esters (3-5). Effects produced by, e.g. di(2-ethylhexyl) phthalate (DEHP) on mitochondrial function and energy metabolism *in vivo* are also produced (*in vitro*) by either *mono*-2-ethylhexyl phthalate or 2-ethylhexanol or their oxidation products (6,7). Oral exposure to less than massive amounts of DEHP, the most thoroughly studied of the phthalate diesters, does not result in exposure of internal organs to intact diester since hydrolysis is very rapid in lung and intestines (8,9). The organs that are most likely to be exposed to high levels of intact phthalate diester—skin and gastrointestinal tract—are not considered target organs for adverse biological effects.

It is important to recall that at this point in time no biological effect of phthalate diesters has been linked to any specific metabolite. The primary metabolites (monoester and alcohol) are each rapidly oxidized to a variety of more polar products *in vivo* (10,11) and *in vitro* (12), any or all of which products may be biologically active. None of these polar metabolites have been tested individually for their biological effects, as none of them (except 2-ethylhexanoic acid) (13) is commercially available in quantities sufficient for testing.

The excreted metabolites of DEHP consist primarily of terminal oxidation products (diacids, ketoacids) in urine from rodents (rats and mice), but primarily of unoxidized or minimally oxidized (mono-2-ethylhexyl phthalate, hydroxyacid) products in urine from primates (African green monkey, humans) (14). Besides the dramatic species differences, there are also major differences between both elimination rates and metabolic profiles when young and old animals of the same species are compared (10,15).

For these reasons it is essential that the metabolism of phthalate esters be understood in some detail. The possibility exists that the adverse biological effects of some phthalate esters, even including the tumor promotion by DEHP (16), may be associated with metabolites not produced to a significant extent by some species (such as humans), or only produced by members of a species whose metabolic capabilities have been altered by age, disease, or exposure to enzyme inducers. The

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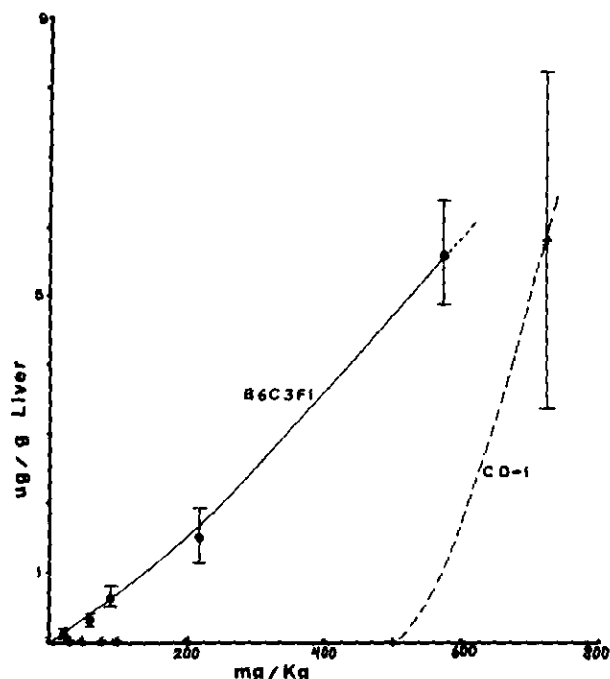
FIGURE 1. Absorption of DEHP in mice. Single oral (gavage) doses of [7-^{14}C]-DEHP were given to CD-1 or B6C3F$_1$ mice in corn oil in triplicate. The levels of ^{14}C-DEHP 6 hr later were determined in the livers by extraction, chromatography on Florisil, and preparative TLC as described previously (14).

first step in comprehending these relationships is to elucidate the metabolism of phthalate esters in normal animals, which is the subject of the present paper. Factors that can alter metabolism and identification of the particular metabolites responsible for particular biological effects remain essential studies for the future.

Absorption Thresholds

We have previously reported (14) that there is a relatively discrete threshold for single oral dosages of DEHP in rats, below which intact diester does not reach the liver but above which there is a rapidly increasing dose-dependent absorption of intact diester. Attempts to detect such a phenomenon in mice did not give clear-cut results (Fig. 1). There may have been such a threshold in CD-1 random-bred mice, but, if so, it was at such a high dose level that we had only a single experimental point above that level in the study. In contrast, there did not appear to be a threshold effect in B6C3F$_1$ mice. Levels of intact, ^{14}C-labeled DEHP reaching the livers was a dose-dependent, nearly linear function of administered DEHP between 20 mg/kg and 575 mg/kg. Levels of ^{14}C-DEHP in the livers were measured 6 hr after dosing, since that was the time at which total ^{14}C in the livers was maximum. An apparent absorption threshold for intact DEHP may exist in Fischer 344 rats (14) and CD-1 mice, but the evidence does not support the existence of one in B6C3F$_1$ mice.

Carcinogenesis bioassays of DEHP in rats have in the past been negative when dosage levels were below the apparent threshold for absorption of intact diester (17) and positive in the only reported bioassay to exceed this threshold (18) and persist above it for two years. DEHP was positive in a carcinogenesis bioassay in B6C3F$_1$ mice (18), the species in which we do not find an absorption threshold (i.e., intact DEHP would be absorbed to some extent even at relatively low doses). Thus the possibility exists that intact DEHP (as diester) must reach the livers of rats and mice in order to produce carcinogenesis, but the available data are inconclusive. There are no data available concerning possible absorption thresholds in humans. However, human exposure to DEHP is often via blood transfusions (19), in which case one would indeed expect intact DEHP to reach the liver. This would not constitute a chronic exposure in most cases, so the relevance to potential carcinogenesis is unclear.

Intermediary Metabolism

The conversion of phthalate diesters to water-soluble excretion products involves more than one metabolic pathway. The pathway followed by phthalate esters whose alcohol portions contain an aliphatic double bond is clearly different from that followed by the more common phthalate plasticizers having saturated aliphatic chains (20). Only the latter will be considered here. Although the basic steps in the pathway are probably the same for a variety of phthalate diesters (21), the spectrum of metabolites is especially complex in the case of DEHP (because of the branched chains). Therefore DEHP will be emphasized to illustrate metabolic capabilities.

Rats and mice differ in their elimination of DEHP metabolites most conspicuously in that mice excrete the oxidation products mainly in the form of glucuronide conjugates, while rats (several strains) do not appear to excrete DEHP metabolites as conjugates (14). It should be noted, however, that rats do excrete glucuronide conjugates of the metabolites of di(n-butyl) phthalate (22). With this exception in the case of rats, there is no reason to suspect that functionally equivalent pathways for metabolism of DEHP differ significantly in any higher species from fish (23) to humans (24). What differences exist appear to be quantitative rather than qualitative, except possibly in the detailed stereochemistry of some of the enzymes involved (10).

The obligatory first step in the metabolism of DEHP is hydrolysis to MEHP plus 2-ethylhexanol. At least 98% of the ^{14}C present in urine of rats given carbonyl-^{14}C-labeled DEHP either orally or IV (25) has been accounted for in the form of some 20 metabolites, none of which retained both ester functions (10). Moreover, it has been reported that all of the urinary metabolites of ^{14}C-DEHP are also found (^{14}C-labeled) in urine of rats given ^{14}C MEHP (10). In addition to the 20 known metabolites DEHP derived from MEHP and retaining the o-phthal ate moiety (10), at least seven metabolites produced rats from 2-ethylhexanol have been identified (11).

Table 1. Distribution of DEHP hydrolase activity in various tissues of CD rats.[a]

	DEHP hydrolase	
Tissue homogenate	U/mg protein	U/g tissue
Intestinal mucosa	0.86	83
Liver	0.48	144
Kidney	0.15	45
Lung	0.07	15
Plasma	0.27	17
Pancreas	54.9	34,400
Skin	0.41	15
Adipose	0.23	1.4

[a] Hydrolysis of DEHP to MEHP followed radiochemically at the pH optimum for each tissue, using cholate-solubilized DEHP. One unit corresponds to the hydrolysis of 1 nmole/min at 37°C. Data of Albro and Thomas (8).

the carbon chain of 2-ethylhexanol is ultimately capable of being metabolized to CO_2 (11,26), only the metabolites derived from MEHP will be considered in what follows.

The enzyme(s) responsible for the hydrolysis of DEHP to MEHP and 2-ethylhexanol is (are) found in all tissues surveyed (Table 1) but especially in the pancreas (8). The enzyme (trivial name, nonspecific lipase, E.C. 3.1.1.-) has been purified from rat pancreas and its catalytic mechanism determined (27). The enzyme requires that the ester substrate be presented in the form of an anionic micelle (28), and can carry the hydrolysis of DEHP to completion (no product inhibition). MEHP is not hydrolyzed to phthalic acid by this enzyme. The only esterase thus far reported that will accept MEHP as substrate

was located in liver microsomes (8), and is presumably responsible for the production of the very minor amount of free phthalic acid found in rat urine (14) and the considerably greater amount found in mouse urine (14) following administration of DEHP.

Following hydrolysis of DEHP, MEHP undergoes a series of oxidations *in vivo* as summarized in Figure 2 (10). Only the side chain of MEHP is shown in the figure; there appears to be no alteration of the aromatic ring in mammals (10). Figure 2 is intended to show metabolic relationships only; it should not be taken as a specific pathway. The currently postulated functional pathway for metabolism of DEHP in rodents is illustrated in general terms in Figure 3. Comparison of Figures 2 and 3 reveals that, because of the existence of two chain terminations on the ethylhexyl moiety, several distinct metabolites can result from each type of metabolic process. Characterization of the individual metabolites has been presented previously (10) and will not be belabored here.

The second stage in the (oxidative) metabolism of DEHP, introduction of hydroxyl groups at various positions of the C-8 side chain of MEHP, is catalyzed by NADPH-dependent microsomal monooxygenases analogous (or identical) to the cytochrome P-450 associated fatty acid ω- and $(\omega - 1)$ hydroxylases (12). This activity has been measured in rat liver and kidney and rabbit lung (but not rat lung), as summarized in Table 2. Selective effects of inhibitors and inducers, plus determination of kinetic constants, indicated that at least two different monooxygenases act on MEHP in rat liver (12).
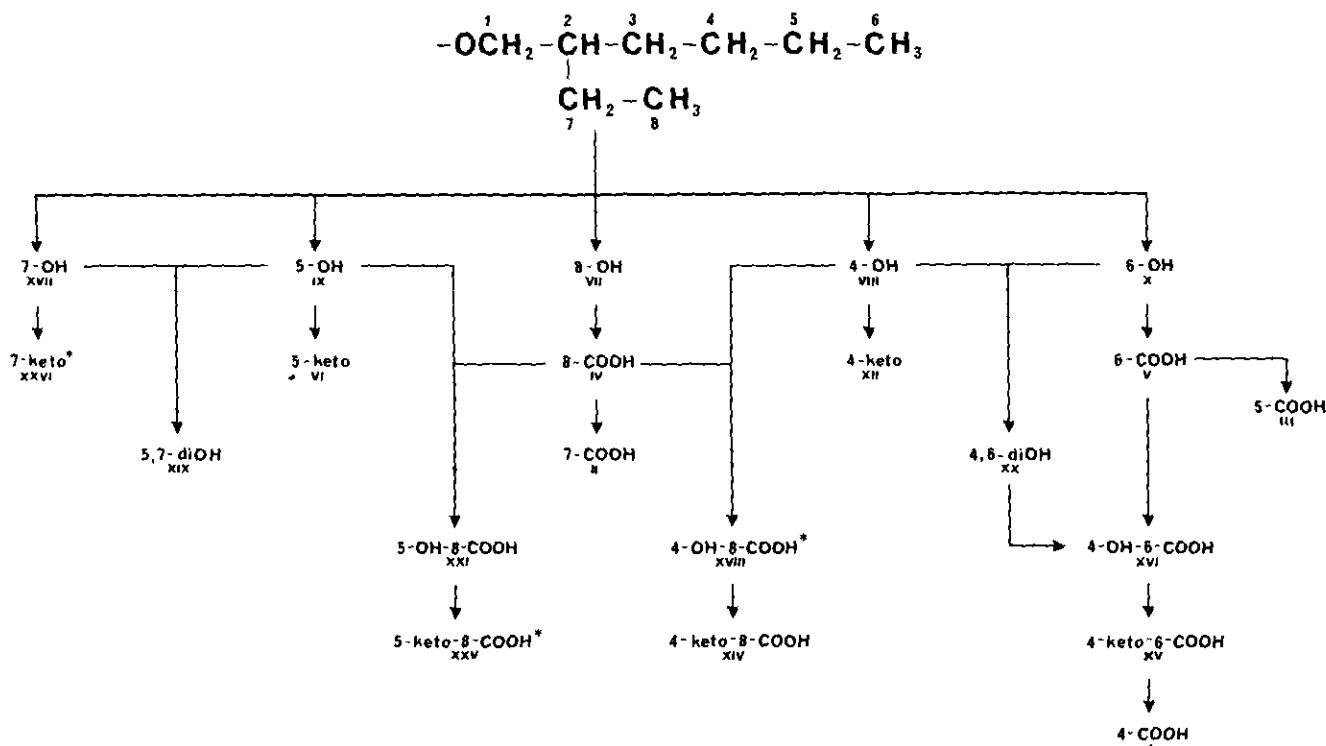

FIGURE 2. Metabolites produced from MEHP by rats *in vivo* and excreted in the urine. Only the ethylhexyl chain and its metabolic alterations are shown, but it should be assumed that the chain is esterified to one of the two carboxylate groups of o-phthalic acid (10).
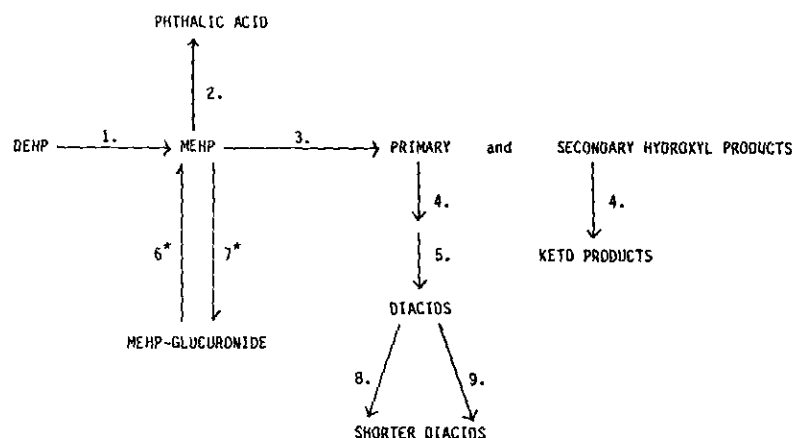
FIGURE 3. Postulated pathway for metabolism of DEHP in mammals: (1) nonspecific lipase; (2) esterase (primarily microsomal); (3) microsomal monooxygenase + NADPH + O₂; (4) alcohol dehydrogenase + NAD (cytosolic); (5) aldehyde dehydrogenase + NAD; (6) β-glucuronidase (reaction substrate may also involve other metabolites); (7) UDP-glucuronyltransferase + UDPG (may also accept other metabolites as substrates); (8) α-oxidation enzymes and cofactors, mitochondria; (9) β-oxidation enzymes and cofactors, mitochondria and/or peroxisomes.

This enzyme system has not been studied in microsomes from mice as yet.

Hydroxylation of MEHP is in direct competition with hydrolysis to phthalic acid by microsomal esterase (Fig. 3) and also with conjugation by UDP-glucuronyltransferase. In spite of the fact that rats do not excrete detectable amounts of DEHP metabolites in the form of glucuronides, microsomes from both rats and mice catalyze the glucuronide conjugation of MEHP as well as of mono-n-butyl phthalate, as shown in Table 3. The reaction involves UDP-glucuronic acid and microsomes, but apparently no other cofactors are required. Microsomes from CD rats are only about half as active as those from B6C3F₁ mice when MEHP is the substrate, while both sources of microsomes are equally active with butyl phthalate as substrate. The reverse reaction is catalyzed by β-glucuronidase, the level of which was much higher in rat liver than in mouse liver (Table 4). Levels of this enzyme were comparable in rat and mouse urine (29).

We are just beginning to study in detail the further oxidation of hydroxylated MEHP. At the moment all that can be said is that the hydroxylated metabolites are oxidized to keto- and carboxyl-containing products by an enzyme or enzymes in the post-microsomal supernatant fraction of rat liver homogenates, and that NAD is involved in the reaction (unpublished observations). Beyond this, there are preliminary indications of a reaction between those metabolites containing a terminal, aliphatic carboxyl group and reduced coexzyme A in the presence of ATP, MgCl₂, and acyl coenzyme A synthetase purified from beef liver. This reaction may be preparatory to α- and/or β-oxidation of the carboxy-terminated metabolites as postulated in Figure 3.

Elimination–Excretion

Elimination kinetics for DEHP has been studied in several animal species (30–32), but unfortunately the mouse is not one of them. Crude measurements have been made, generally at a single dose level and at a few time points, but a careful pharmacokinetic study in the mouse is lacking, so rat and mouse can not be compared in this regard.

Metabolite distributions in urine tend to be characteristic of a given species and relatively independent of dose

Table 2. Distribution of MEHP hydroxylase activity in uninduced microsomes from different sources.[a]

| Source | Hydroxylation pmole/min/mg protein | | |
	ω	ω − 1	ω − 2
Rat liver	143	542	207
Rat kidney cortex	125	223	152
Rat lung	ND[b]	ND	ND
Rabbit lung	29	4	8

[a] Production of metabolites X (ω), IX (ω - 1), and VII (ω - 2) (for structures see Fig. 2) from MEHP in vitro with purified microsomes in the presence of an NADPH generating system. Taken from Albro et al. (12) which gives details of the assay.

[b] ND = none detected.

Table 3. Phthalate monoester: UDP-glucuronyltransferase activity in microsomes from CD rats and B6C3F₁ mice.[a]

| Incubation conditions | UDPG transferase activity, pmole/min/mg protein | |
	Rat	Mouse
Complete, + MEHP[b]	276	447
Complete, + MBP	198	202
Minus digitonin, + MEHP	383	110
Complete, boiled microsomes, + MEHP	27	—
Minus UDPD, + MEHP	13	—

[a] Each tube received 0.75 mL of 0.1 M Tris HCl, pH 7.4, containing 1.27 mg MgCl₂/mL, 0.1 mL of microsome preparation at 10 mg protein/mL, 0.25 M sucrose, 0.1 mL of UDP-glucuronic acid (UDPG) at 60 μmole/mL in water, and 0.1 μCi (0.1 μmole) of either MEHP or mono-n-butyl [7-¹⁴C]-phthalate (MBP) in 10 μL of DMSO. Incubation was 30 min at 37°C, the formation of glucuronide conjugate being monitored by radio-HPLC as described previously (29).

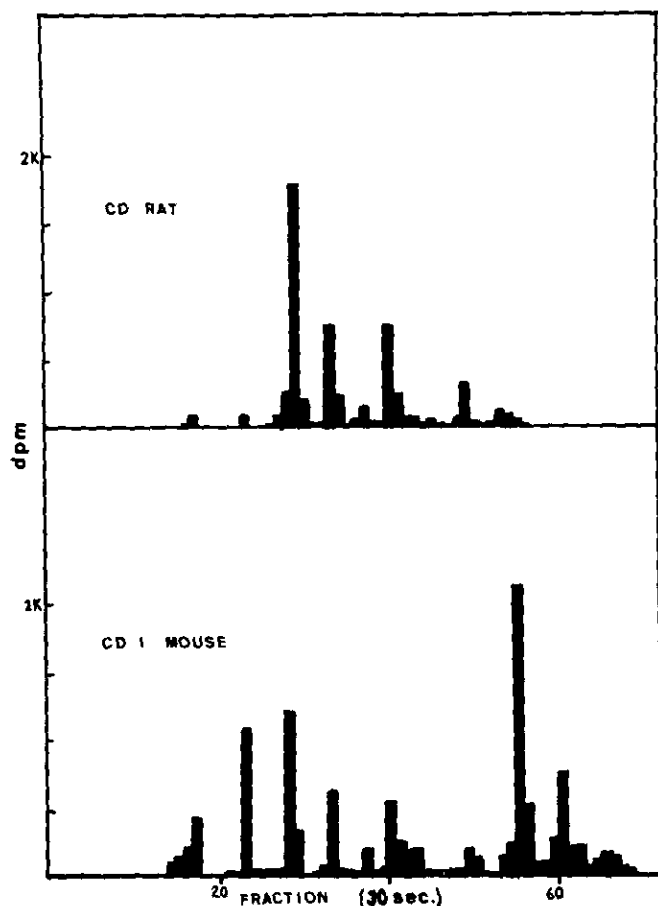[b] The complete system includes 0.2% digitonin as hypothetical activator.

FIGURE 4. HPLC radiochromatograms of diazomethane-treated urinary metabolites of DEHP from rat and mouse. Chromatography on S5CN with a nonlinear gradient of tetrahydrofuran into heptane as described previously (29).

(though not independent of route of exposure) (25). A comparison of the profiles of DEHP metabolites in urine from CD rats and CD-1 mice is illustrated in Figure 4. DEHP labeled with [14]in the carbonyl position was administered orally in corn oil by gavage, urine was collected for 48 hr, the metabolites were stripped from acidified urine using XAD-2 resin, esterified with diazomethane, and fractionated by HPLC on a Spherisorb S5CN nitrile column with a heptane:tetrahydrofuran gradient, all as described previously (29). Fractions (30 sec each) were collected and radioassayed by liquid scintillation counting to produce the profiles shown. The me-

Table 4. Levels of β-glucuronidase activity in liver and urine of CD rats and B6C3F1 mice[a].

| | β-glucuronidase activity, nmole/min[b] | |
	Liver[c]	Urine
Rats	4.18	2.83
Mice	1.57	3.66

[a] Using phenolphthalein glucuronide as substrate at pH 4.5, 37°C, means of three animals.
[b] Per mg protein (liver) or per mL urine.
[c] 20000g supernatant of 10% homogenate.

tabolite structures associated with each peak of radioactivity were identified by gas chromatography-mass spectrometry and formation of characteristic derivatives (10).

The mouse urine contained all the metabolites found in rat urine, plus glucuronide ester conjugates of most of them (29). However, after hydrolysis of the conjugates it would be seen that the relative amounts of different metabolites were quite different for the two species (Table 5). Whereas metabolite V, or 2-ethyl-5-carboxypentyl phthalate was by far the most abundant single metabolite in rat urine, its presumed β-oxidation product, 2-ethyl-3-carboxypropyl phthalate predominated in the mouse urine. This suggests that the production of glucuronide conjugates in the mouse does not lead to rapid excretion of less oxidized metabolites than those excreted by rats. The mean oxidation level of the urinary profile of DEHP metabolites in the mouse is not much less than that of the rat. If this mean is expressed in terms of the amount of NAD that must be reduced to produce it, the numbers come out 2.93 mole NAD/mole phthalate in the rat and 2.23 mole/mole in the mouse. These numbers may be contrasted with calculated values of 1.42 mole/mole for the African green monkey and 1.48 mole/mole for human leukemia patients.

Figure 2 also indicates that some of the identified metabolites of DEHP have been oxidized at two points on the ethylhexyl chain. Whether this represents a simultaneous attack or "recycling" is not known; we have not succeeded in producing these metabolites in vitro.

Summary and Discussion

The metabolism of phthalate esters by a variety of laboratory animal species is beginning to be understood, although a number of details remain to be elucidated. The point in the metabolic pathway at which the quantitative differences among species arises, at least in control animals (those not chronically exposed to phthalates), would logically be the point of threefold competition in Figure 3. The proliferation of peroxisomes and mitochondria in rodents exposed chronically to DEHP (2,33),

Table 5. Comparison of metabolite distributions in urine of CD rats and CD-1 mice 24 hr after oral administration of DEHP.

| | Percentage of [14]C[a] | |
Metabolite[b]	Mouse	Rat
MEHP	18.6 ± 2.3	0.1 ± 0.1
Phthalic acid	12.4 ± 1.5	2.5 ± 0.6
I-V (diacids)[c]	20.0 ± 1.9	65.3 ± 7.2
VI (keto)	14.9 ± 2.1	9.5 ± 1.0
VII-X (hydroxy)	21.6 ± 2.7	13.3 ± 1.5
XV-XX (recycled?)	11.5 ± 1.3	9.3 ± 1.1

[a] Mean ± SD (N = 3 each) in total 24 hr urine following administration by gavage of [7-14C]-DEHP in corn oil at a dosage level of 180 mg/kg body weight in both species.
[b] Structrues designated by Roman numerals correspond to the structures summarized in Figure 2 (10).
[c] Metabolites I and V dominate this class, amounting to 16.8 (I) and 1.1 (V) % of total 14C from the mice and 9.4 (I) and 50.7 (V) % from the rats.

although it should increase the capabilities for β-oxidation of aliphatic carboxylates in these species, cannot account for the differences in naive animals as the β-oxidation enzymes increase only several days after DEHP is given.

There are implied "competitive" branch points not shown in Figure 3 that must be considered as well. Excretion of a given metabolite is always potentially in competition with further oxidation of that metabolite. Relative kidney clearance rates, presence or absence of highly water-soluble glucuronide conjugates, and relative K_m values of the oxidative enzymes of different species must all be interacting with the competition between those enzymes that utilize the same substrate to produce the observed differences in endpoint metabolic profiles in different animal species.

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