

Levels of Seven Urinary Phthalate Metabolites in a Human Reference Population

Benjamin C. Blount,¹ Manori J. Silva,¹ Samuel P. Caudill,¹ Larry L. Needham,¹ Jim L. Pirkle,¹ Eric J. Sampson,¹ George W. Lucier,² Richard J. Jackson,¹ and John W. Brock¹

¹National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; ²National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA

Using a novel and highly selective technique, we measured monoester metabolites of seven commonly used phthalates in urine samples from a reference population of 289 adult humans. This analytical approach allowed us to directly measure the individual phthalate metabolites responsible for the animal reproductive and developmental toxicity while avoiding contamination from the ubiquitous parent compounds. The monoesters with the highest urinary levels found were monoethyl phthalate (95th percentile, 3,750 ppb, 2,610 µg/g creatinine), monobutyl phthalate (95th percentile, 294 ppb, 162 µg/g creatinine), and monobenzyl phthalate (95th percentile, 137 ppb, 92 µg/g creatinine), reflecting exposure to diethyl phthalate, dibutyl phthalate, and benzyl butyl phthalate. Women of reproductive age (20–40 years) were found to have significantly higher levels of monobutyl phthalate, a reproductive and developmental toxicant in rodents, than other age/gender groups ($p < 0.005$). Current scientific and regulatory attention on phthalates has focused almost exclusively on health risks from exposure to only two phthalates, di-(2-ethylhexyl) phthalate and di-isononyl phthalate. Our findings strongly suggest that health-risk assessments for phthalate exposure in humans should include diethyl, dibutyl, and benzyl butyl phthalates.

Key words: exposure, glucuronidase, human, metabolism, phthalates, urine. *Environ Health Perspect* 108:979–982 (2000). [Online 1 September 2000]

<http://ehpnet1.niehs.nih.gov/docs/2000/108p972-982blount/abstract.html>

Dialkyl or alkyl aryl esters of 1,2-benzenedicarboxylic acid, commonly called phthalates, are ubiquitous industrial chemicals with a wide range of chemical and toxicologic characteristics. Phthalates are used primarily as plasticizers in flexible polyvinyl chloride (PVC) products such as blood bags and children's toys. Nonpolymeric uses of phthalates as fixatives, detergents, lubricating oils, and solvents lead to their inclusion in numerous and diverse products such as cosmetics and wood finishes. The widespread use of phthalates results in multiple human exposure routes (oral, dermal, inhalation, and intravenous). Phthalates are lipophilic compounds that appear not to bioaccumulate (1). Phthalates are rapidly metabolized to their respective monoesters and further oxidative products, which are glucuronidated and excreted through the urine and feces (1–4).

Animal toxicology of several phthalates has been studied. Di-(2-ethylhexyl) phthalate (DEHP) is a rodent liver carcinogen through a mechanism thought to involve peroxisome proliferation (5); however, carcinogenicity by this mechanism is unlikely to be relevant to humans (6,7). Several phthalates, DEHP, dibutyl phthalate (DBP), and benzyl butyl phthalate (BzBP), are teratogenic in animals (8–10). DBP is also toxic to the testes, possibly through its metabolite, monobutyl phthalate (MBP) (11,12); other phthalate metabolites, monobenzyl phthalate (MBzP) and mono-2-ethylhexyl phthalate

(MEHP), are Sertoli cell toxicants and teratogens in animals (13,14). Furthermore, administration of DBP and DEHP to pregnant rats interferes with normal fetal development in male offspring (15). Regarding reproductive and developmental effects, phthalates vary in potency, with DEHP being the most potent and DBP and BzBP roughly an order of magnitude less potent (8–15).

Based on the varied toxicities of phthalates, internal dose measurements of specific phthalates and their monoester metabolites (16) are important for exposure assessment, and ultimately for accurate human risk assessment. Previous methods for assessing human exposure to phthalates have been subject to laboratory and sample-collection contamination problems from these environmentally ubiquitous compounds (17–20). For this reason, previous measurements of internal phthalate dose have focused on highly exposed people (21,22). As the primary urinary metabolite, phthalate monoesters are useful biomarkers of specific phthalate exposure.

We report the urinary phthalate monoester levels for a human reference population using a new, highly selective technique (23). This analytical approach allows us to directly measure the individual phthalate metabolites responsible for the reproductive and developmental toxicity of phthalates in animals while avoiding contamination from the ubiquitous parent

compound. The metabolites measured are monoethyl phthalate (MEP), MBP, MBzP, mono-*n*-octyl phthalate, MEHP, and mono-3-methyl-5-dimethylhexyl phthalate (monoisononyl, MINP). Commercially used di-isononyl phthalate (DINP) is a technical mixture containing a number of different isomers; therefore, several metabolite isomers are expected. We chose the monoester metabolite of one representative isomer for DINP. Measurement of this single isomer may underestimate exposure to DINP. Current efforts are focused on quantification of additional metabolites of DINP.

Subjects

The urine samples for this study were originally collected from adults during 1988–1994 as part of the Third National Health and Nutrition Examination Survey (NHANES III). Randomly selected urine samples from 289 subjects were analyzed for phthalate monoesters. Urine samples were collected at different times throughout the day and were not first-morning voids. This sampling of the NHANES III population was not designed to be representative of the U.S. population but rather to serve as a reference range for a demographically described group. The population studied comprised noninstitutionalized adults aged 20–60 years (mean \pm SD 37.4 \pm 10.6 years). The gender distribution (56% female) was similar across age groups. Racial distribution was weighted toward minority groups (Caucasian 39%, African American 30%, Mexican American 23%, and other 8%).

Address correspondence to J.W. Brock, National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Highway MS F-17, Atlanta, GA 30341 USA. Telephone: (770) 488-7839. Fax: (770) 488-4609. E-mail: jwb6@cdc.gov

We thank E. Milgram, C. Hodge, N. Malek, and J. Reidy for assistance with methods development and implementation; E. Gunter for providing urinary creatinine analysis; and the National Center for Health Statistics for assistance with demographic information.

This work was partially funded by the National Toxicology Program and the National Institute of Environmental Health Sciences.

Received 26 May 2000; 19 July 2000.

Methods

The method used has been described previously (23). All samples were spiked with $^{13}\text{C}_4$ -labeled phthalate monoesters and 4-methylumbelliferone glucuronide. The samples were then treated with a β -glucuronidase to release the phthalate monoesters from its conjugated form. Deconjugated urine samples were extracted twice with Oasis HLB SPE (Waters Corp., Milford, MA) as described (23) and resuspended in mobile phase. Chromatographic separation by HPLC was followed with tandem mass spectrometry on a triple quadrupole instrument (Finnigan TSQ 7000; Finnigan MAT, San Jose, CA) using atmospheric pressure chemical ionization. Retention times as well as parent-fragment ion combinations have been described previously (23). Levels of 4-methylumbelliferone were monitored as quality control for the deconjugation step. Urinary creatinine was measured with an ASTRA analyzer (Beckman, Brea, CA) based on a Jaffé rate reaction, in which creatinine reacts with picrate in an alkaline solution to form a red creatinine-picric acid complex (24). Results are reported as micrograms phthalate monoester per gram of urinary creatinine. Creatinine adjustment is used to correct for variations in urine volume. Method blanks, quality control samples (spiked human urine), and standards were analyzed along with unknown human urine samples.

This method has been refined to monitor and eliminate monoester contamination by excluding the use of phthalate-containing plastics, prescreening reagents, and labware, and routinely monitoring method and instrument blanks. Phthalate diesters are often components of flexible PVC plastics. Therefore, products containing this polymer were not used. Although the polypropylene and glass components used were unlikely to contain significant amounts of phthalates, we prescreened representative vials, pipette tips, glassware, and sampling cups for phthalate monoester contamination. As an additional precaution, method blanks were analyzed in parallel with unknown samples. Insignificant phthalate monoester levels were found in blanks (typically < 0.5% of the mean level found in human samples). A blank containing > 5 ppb of any analyte resulted in rejection of all analytical results acquired on that day and an effort to identify the source of the contamination.

One source of contamination that had to be eliminated was diester lipase activity in the glucuronidase enzyme preparation (23). We enzyme-treated artificial urine samples (25) with and without spiked phthalate diesters to determine if the presence of phthalate diesters would cause an artifactual increase in phthalate monoester levels. When samples spiked

with phthalate diesters were incubated with β -glucuronidase/sulfatase (*Helix pomatia*, H-1), significant amounts of the corresponding phthalate monoesters were formed (MEP, MBP, MBzP, and MEHP). These enzymes, *H. pomatia* β -glucuronidase/sulfatase (from two vendors), were contaminated with an enzymatic activity that hydrolyzed phthalate diesters to generate phthalate monoesters; nonspecific lipases with this activity are common (26). Given the abundance of phthalate diesters in the environment (including the laboratory), the use of the *H. pomatia* β -glucuronidase/sulfatase should be avoided for analysis of phthalate monoesters. *Escherichia coli* β -glucuronidase (K12; Roche Biomedical, Indianapolis, IN) has excellent glucuronidase activity and no measurable lipase activity on phthalate diesters. Although this enzyme lacks sulfatase activity, no phthalate conjugates other than glucuronides have been detected in human urine (27). For previously published phthalate monoester measurements, *H. pomatia* β -glucuronidase/sulfatase was used; therefore artifactual high results may be present (3,22).

Results and Discussion

Our study provides an assessment of human exposure to phthalates. Phthalate monoester levels in human urine vary widely (Table 1); urinary creatinine adjustment reduces this variation somewhat (Table 2). In this reference population, the phthalate monoesters with the highest urinary levels found are MEP (16,200 ppb, 6,790 $\mu\text{g/g}$ creatinine), MBP (4,670 ppb, 2,760 $\mu\text{g/g}$ creatinine), and MBzP (1,020 ppb, 540

$\mu\text{g/g}$ creatinine), which reflect exposure to diethyl phthalate (DEP), DBP, and BzBP. DEP and DBP are used extensively in products with volatile components such as perfumes, nail polishes, and hair sprays, possibly leading to inhalation and efficient absorption through the lungs. Dermal absorption also occurs at a significant rate for phthalates with short side chains such as DEP, DBP, and BzBP (28).

The highest levels of MEHP in this study (67 ppb, 192 $\mu\text{g/g}$ creatinine) agree with levels found previously in urine from occupationally exposed subjects (22). The median MEHP levels for this general reference population were 70-fold lower than the highest values. In urine, the more lipophilic phthalate monoesters, such as MEHP and MINP, were generally found at lower levels than other monoesters. The relatively low median MEHP and MINP levels suggest either low exposures to DEHP and DINP, storage in adipose tissue, or metabolism and excretion through another pathway. Limited data suggest that DEHP is partially excreted in the feces (1); because of similar lipophilicity, DINP may also be excreted fecally. Further complicating assessment, DINP consists of a mixture of phthalate isomers that yield a large number of monoester metabolites. Only one of these metabolites, mono-3-methyl-5-dimethylhexyl phthalate, was measured in urine and was assumed to be representative of the presence of other DINP metabolites. In any event, these data on monoesters indicate that the internal dose of MEP, MBP, and MBzP is probably much higher than that of MINP and MEHP.

Table 1. Total urinary phthalate monoester concentrations (nanograms monoester per milliliter urine).

Phthalate	Percentile							Geometric mean
	Min	5th	25th	50th	75th	95th	Max	
Ethyl	< LOD	26.1	119	305	1,110	3,750	16,200	345
Benzyl	1.4	4.2	11.0	21.2	42.2	137	1,020	22.6
Butyl	2.2	6.9	19.4	41.0	82.3	294	4,670	41.5
Cyclohexyl	< LOD	< LOD	< LOD	< LOD	< LOD	8.6	13.7	0.3
2-Ethylhexyl	< LOD	< LOD	1.4	2.7	7.0	21.5	66.6	3.5
Isononyl	< LOD	< LOD	< LOD	< LOD	< LOD	7.3	79.7	1.5
Octyl	< LOD	< LOD	< LOD	< LOD	< LOD	2.3	30.5	0.6

Abbreviations: LOD, limit of detection; Max, maximum; Min, minimum. LODs for phthalates (ng/mL) are as follows: MEP, 1.0; MBP, 0.6; MBzP, 0.8; monocyclohexyl phthalate, 0.7; MEHP, 1.2; MNP, 0.8; and mono-*n*-octyl phthalate, 0.9.

Table 2. Total urinary phthalate monoester concentrations (micrograms monoester per gram urinary creatinine).

Phthalate	Percentile							Geometric mean
	Min	5th	25th	50th	75th	95th	Max	
Ethyl	< LOD	30.2	133	280	704	2,610	6,790	345
Benzyl	2.1	5.0	10.8	19.5	36.9	91.9	544	20.2
Butyl	1.6	9.3	19.4	33.4	60.1	162	2,760	36.9
Cyclohexyl	< LOD	< LOD	< LOD	< LOD	0.4	1.0	10.3	0.3
2-Ethylhexyl	< LOD	< LOD	1.3	2.7	5.2	15.2	192	3.0
Isononyl	< LOD	< LOD	< LOD	< LOD	< LOD	6.8	90.3	1.3
Octyl	< LOD	< LOD	< LOD	< LOD	< LOD	2.1	27.0	0.5

Abbreviations: LOD, limit of detection; Max, maximum; Min, minimum.

Glucuronidation has been hypothesized to mitigate phthalate monoester toxicity in rodents (29). To assess the degree of phthalate monoester conjugation, we analyzed a subset of 73 samples with and without β -glucuronidase treatment. Low urinary levels of monoester before deglucuronidation suggest that MBP and MBzP were present predominantly as the glucuronide form. However, a small portion (5%) of the reference population had substantially higher percentages of unconjugated MBP than the rest of the population (67% above the next lowest value). These differences in MBP glucuronidation could be caused by enzymatic saturation due to a large recent dose of parent diester phthalate. Arguing against simple saturation, urinary MBP levels did not correlate with the ratio of MBP/MBP-glucuronide. Although based on limited data, this observation underscores the potential variability in the human metabolism of phthalate monoesters and thereby variable monoester exposure and toxicity.

For analytes found in > 75% of subjects (MEHP, MEP, MBzP, and MBP), we examined log-transformed creatinine-adjusted levels by analysis of variance models to assess effects from selected demographic factors: age (four groups), sex, race (four groups), socioeconomic status (two groups), urban/rural residence, and education (two groups). All comparison cells described contain > 50 people. Significant differences in creatinine-adjusted values between groups were not caused by differences in urinary creatinine levels. Because of the large number of statistical tests performed on our data, the effects of demographic factors on urinary phthalate levels should be considered for generating hypotheses only.

After adjustment for the effects of other factors, creatinine-adjusted MEP levels

increased on average by 1.7% ($p < 0.02$) for every yearly increase in age; conversely, creatinine-adjusted MBzP levels decreased by 1% ($p < 0.04$) for the same increase in age. Subjects who had completed ≤ 12 years of formal education had higher levels of MBzP (22 $\mu\text{g/g}$ creatinine) than subjects with more formal education (16 $\mu\text{g/g}$ creatinine; $p < 0.01$). Further statistical testing indicated that MBP levels in non-Hispanic whites also differed between the two education groups (≤ 12 years: 53 $\mu\text{g/g}$ creatinine; > 12 years: 28 $\mu\text{g/g}$ creatinine; $p < 0.001$), whereas MBP levels in non-Hispanic blacks and Hispanics were comparable regardless of education (33 $\mu\text{g/g}$ creatinine). Further statistical testing also showed that rural females had significantly higher urinary levels of MBzP (26 $\mu\text{g/g}$ creatinine) than rural males (14 $\mu\text{g/g}$ creatinine; $p < 0.001$), urban females (19 $\mu\text{g/g}$ creatinine; $p < 0.02$), and urban males (18 $\mu\text{g/g}$ creatinine; $p < 0.02$).

Of concern, women of childbearing age (20–40 years) had significantly higher urinary levels of MBP (46.9 $\mu\text{g/g}$ creatinine) than other sex/age groups (31.4 $\mu\text{g/g}$ creatinine; $p = 0.003$). Furthermore, six of the eight highest MBP levels were found in these women. Creatinine adjustment did not account for this effect. Nine of the highest 10 noncreatinine-adjusted values were found in women of reproductive age. Ten subjects had urinary MBP > 300 $\mu\text{g/g}$ creatinine, including three women of reproductive age with levels > 2,000 $\mu\text{g/g}$ creatinine (Figure 1). A similar analysis for urinary MBzP did not indicate a difference, but a more detailed look at the rural women with high levels of MBzP suggests that rural women of childbearing age have higher levels (31.6 $\mu\text{g/g}$ creatinine) than older (41–60 years) rural women (21.1 $\mu\text{g/g}$ creatinine). The small study size and nonrepresentative nature of this sample population limits the applicability of these statistical associations. However, these findings do indicate the possibility of significant demographic variations in exposure and/or metabolism.

From a public health perspective, these data provide evidence that phthalate exposure is both higher and more common than previously suspected. Exposure data for phthalates is critically important for human risk assessment, especially among potentially susceptible populations. Although DEHP and DINP are produced in the largest quantities, these reference range data indicate a substantial internal human dose of DBP, DEP, and BzBP. MBP and MBzP are of particular concern because of their developmental and reproductive toxicity in animals (12–15). Therefore, assessments of health risk from exposures to phthalates should include exposures to DBP, DEP, and BzBP.

REFERENCES AND NOTES

- Schmid P, Schlatter C. Excretion and metabolism of di(2-ethylhexyl)phthalate in man. *Xenobiotica* 15:251–256 (1985).
- Albro PW, Thomas R, Fishbein L. Metabolism of diethylhexyl phthalate by rats. Isolation and characterization of the urinary metabolites. *J Chromatogr* 76:321–330 (1973).
- Dirven HA, van den Broek PH, Jongeneelen FJ. Determination of four metabolites of the plasticizer di(2-ethylhexyl)phthalate in human urine samples. *Int Arch Occup Environ Health* 64:555–560 (1993).
- Ward JM, Diwan BA, Oshima M, Hu H, Schuller HM, Rice JM. Tumor-initiating and promoting activities of di(2-ethylhexyl) phthalate *in vivo* and *in vitro*. *Environ Health Perspect* 65:279–291 (1986).
- David RM, Moore MR, Cifone MA, Finney DC, Guest D. Chronic peroxisome proliferation and hepatomegaly associated with the hepatocellular tumorigenesis of di(2-ethylhexyl)phthalate and the effects of recovery. *Toxicol Sci* 50:195–205 (1999).
- Doull J, Cattle R, Elcombe C, Lake BG, Swenberg J, Wilkinson C, Williams G, van Gemert M. A cancer risk assessment of di(2-ethylhexyl)phthalate: application of the new U.S. EPA Risk Assessment Guidelines. *Regul Toxicol Pharmacol* 29:327–357 (1999).
- Ema M, Amano H, Itami T, Kawasaki H. Teratogenic evaluation of di-*n*-butyl phthalate in rats. *Toxicol Lett* 69:197–203 (1993).
- Ema M, Itami T, Kawasaki H. Teratogenic phase specificity of butyl benzyl phthalate in rats. *Toxicology* 79:11–19 (1993).
- Shiota K, Chou MJ, Nishimura H. Embryotoxic effects of di-2-ethylhexyl phthalate (DEHP) and di-*n*-butyl phthalate (DBP) in mice. *Environ Res* 22:245–253 (1980).
- Foster PM, Thomas LV, Cook MW, Gangolli SD. Study of the testicular effects and changes in zinc excretion produced by some *n*-alkyl phthalates in the rat. *Toxicol Appl Pharmacol* 54:392–398 (1980).
- Heindel JJ, Powell CJ. Phthalate ester effects on rat Sertoli cell function *in vitro*: effects of phthalate side chain and age of animal. *Toxicol Appl Pharmacol* 115:116–123 (1992).
- Gray TJ, Beaman JA. Effect of some phthalate esters and other testicular toxins on primary cultures of testicular cells. *Food Chem Toxicol* 22:123–131 (1984).
- Ema M, Harazono A, Miyawaki E, Ogawa Y. Developmental toxicity of mono-*n*-benzyl phthalate, one of the major metabolites of the plasticizer *n*-butyl phthalate, in rats. *Toxicol Lett* 86:19–25 (1996).
- Gray LE Jr, Wolf C, Lambright C, Mann P, Price M, Cooper RL, Ostby J. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, *p,p'*-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. *Toxicol Ind Health* 15:94–118 (1999).
- Pirkle JL, Sampson EJ, Needham LL, Patterson DG, Ashley DL. Using biological monitoring to assess human exposure to priority toxicants. *Environ Health Perspect* 103(suppl 3):45–48 (1995).
- Harvan DJ, Hass JR, Albro PW, Friesen MD. Mass spectrometry of di-(2-ethylhexyl)phthalate metabolites. *Biomed Mass Spectrom* 7:242–246 (1980).
- Luster MI, Albro PW, Chae K, Clark G, McKinney JD. Radioimmunoassay for mono-(2-ethylhexyl) phthalate in unextracted plasma. *Clin Chem* 24:429–432 (1978).
- Albro PW, Jordan S, Corbett JT, Schroeder JL. Determination of total phthalate in urine by gas chromatography. *Anal Chem* 56:247–250 (1984).
- Brock JW, Burse VW, Ashley DL, Najam AR, Green VE, Korver MP, Powell MK, Hodges CC, Needham LL. An improved analysis for chlorinated pesticides and polychlorinated biphenyls (PCBs) in human and bovine sera using solid-phase extraction. *J Anal Toxicol* 20:528–536 (1996).
- Plonait SL, Nau H, Maier RF, Wittfoht W, Obladen M. Exposure of newborn infants to di-(2-ethylhexyl)-phthalate and 2-ethylhexanoic acid following exchange transfusion with polyvinylchloride catheters. *Transfusion* 33:598–605 (1993).
- Ching NP, Jham GN, Subbarayan C, Grossi C, Hicks R, Nealon TF Jr. Gas chromatographic quantitation of two plasticizers contaminating intravenous fluids stored in plastic containers. *J Chromatogr* 225:196–201 (1981).

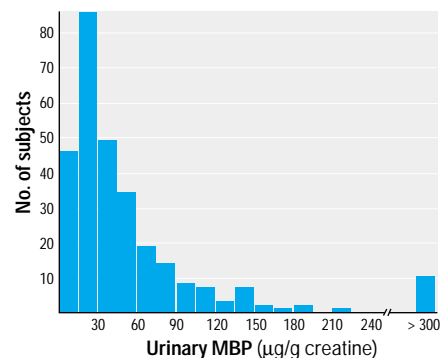


Figure 1. Urinary MBP distribution in a human reference population. The creatinine-adjusted MBP levels in spot urine samples were plotted for 289 subjects from the Third National Health and Nutrition Examination Survey (NHANES III). Ten subjects (predominantly women of reproductive age) had urinary MBP levels > 300 $\mu\text{g/g}$ creatinine (312, 433, 652, 926, 956, 962, 1,745, 2,052, 2,260, and 2,763 $\mu\text{g/g}$ creatinine).

22. Dirven HA, van den Broek PH, Arends AM, Nordkamp HH, de Lepper AJ, Henderson PT, Jongeneelen FJ. Metabolites of the plasticizer di(2-ethylhexyl)phthalate in urine samples of workers in polyvinylchloride processing industries. *Int Arch Occup Environ Health* 64:549-554 (1993).
23. Blount BC, Milgram KE, Silva MJ, Malek NA, Reidy JA, Needham LL, Brock JW. Quantitative detection of eight phthalate metabolites in human urine using HPLC-APCIMS/MS. *Anal Chem* (in press). Available: <http://pubs.acs.org/subscribe/journals/ancham/jtext.cgi?ancham/asap/html/ac000422r.html> [cited 11 August 2000].
24. Gunter EW, Lewis BL, Koncikowski SM. Laboratory methods used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. Hyattsville, MD:Centers for Disease Control and Prevention, 1996.
25. Gustafsson JE, Uzqueda HR. The influence of citrate and phosphate on the Mancini single radial immunodiffusion technique and suggested improvements for the determination of urinary albumin. *Clin Chim Acta* 90(3):249-257 (1978).
26. Albro PW, Thomas RO. Enzymatic hydrolysis of di(2-ethylhexyl) phthalate by lipases. *Biochim Biophys Acta* 306:380-390 (1973).
27. Albro PW, Corbett JT, Schroeder JL, Jordan S, Matthews HB. Pharmacokinetics, interactions with macromolecules and species differences in metabolism of DEHP. *Environ Health Perspect* 45:19-25 (1982).
28. Elsis AE, Carter DE, Sipes IG. Dermal absorption of phthalate diesters in rats. *Fundam Appl Toxicol* 12:70-77 (1989).
29. Foster PM, Cook MW, Thomas LV, Walters DG, Gangolli SD. Differences in urinary metabolic profile from di-*n*-butyl phthalate-treated rats and hamsters. A possible explanation for species differences in susceptibility to testicular atrophy. *Drug Metab Dispos* 11:59-61 (1983).

Changing Leads into Buyers Is a Matter of Perspective



Advertisements in EHP reach thousands of top scientists, research administrators, industrial managers, and public health workers around the world with the power to buy your products and services. Let EHP help you show them what you've got!

- *laboratory instruments*
- *equipment and supplies*
- *computer software and hardware*
- *laboratory animals and chemicals*
- *environmentally preferable products*
- *scientific consulting services*
- *research and information services*

Call 919-541-5466 or e-mail surak@niehs.nih.gov for rate information.