

Supplementary Table S1. Effects of long-term DEHP exposure on male rats' liver enzyme activities and fatty acid levels (means \pm SD, $n = 10$)

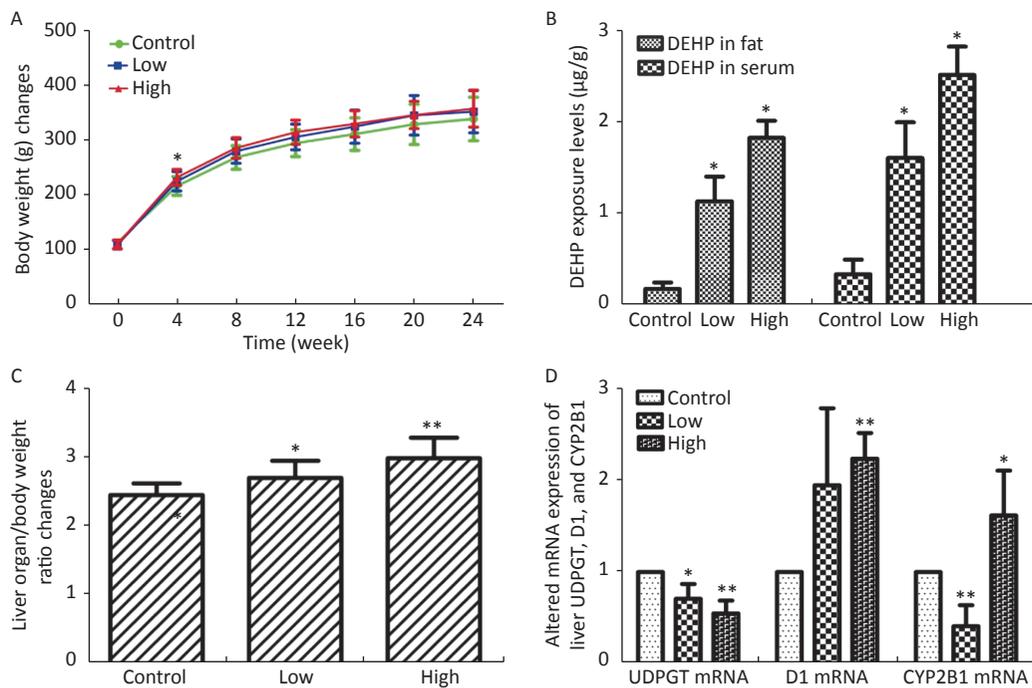
Groups	ALT (U/L)	AST (U/L)	TC (mmol/L)	TG (mmol/L)	HDL (mmol/L)
C	108.53 \pm 7.31	35.89 \pm 3.67	4.89 \pm 1.46	1.89 \pm 0.16	1.45 \pm 0.26
M	110.32 \pm 15.28 ^b	37.28 \pm 8.15 ^b	5.32 \pm 2.08	2.52 \pm 0.87	1.54 \pm 0.68
H	140.32 \pm 10.18 ^a	55.79 \pm 4.62 ^a	6.89 \pm 0.36 ^a	3.24 \pm 0.48 ^a	2.51 \pm 0.3 ^a

Note. ^a $P < 0.05$ compared to group C. ^b $P < 0.05$ compared to group M. C: Control group, 0 mg/(kg-day); M: Low-dose DEHP group, 300 mg/(kg-day); H: High-dose DEHP group, 600 mg/(kg-day). Abbreviations: DEHP, di (2-ethylhexyl) phthalate; ALT, alanine aminotransferase; AST, aspartic transaminase; TC, Serum total cholesterol; TG, Triglyceride; HDL, High-density lipoprotein.

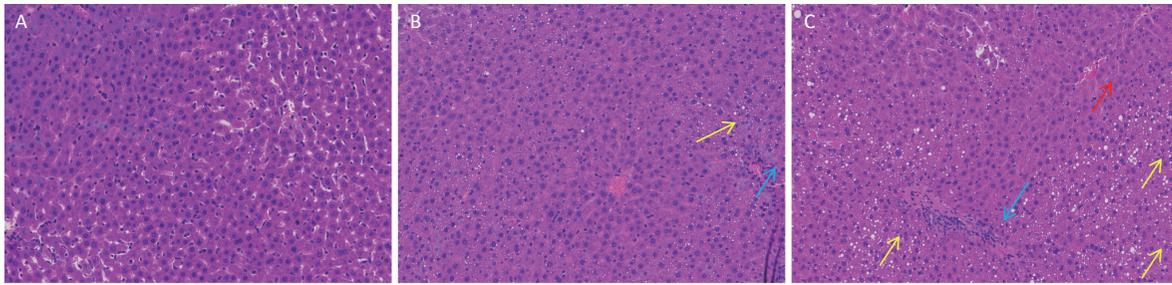
Supplementary Table S2. Biomarkers detected in positive ESI mode in male rats serum (mean \pm SD, $n = 10$)

Groups	PC [18:1(11Z)/18:4(6Z,9Z,12Z,15Z)]	LysoPC (20:0/0:0)	LysoPE (22:0/0:0)	LysoPE (P-18:0/0:0)	LysoPC [20:1(11Z)/0:0]	LysoPC (18:0/0:0)	LysoPC [P-18:1(9Z)/0:0]
C	18.49 \pm 9.34 ^c	32.53 \pm 3.08 ^d	43.92 \pm 11.54 ^d	21.43 \pm 2.25 ^d	165.97 \pm 34.73 ^d	562.56 \pm 47.04 ^d	42.68 \pm 3.62 ^d
M	14.02 \pm 7.67	17.99 \pm 3.67 ^b	0.00 \pm 0.00 ^b	16.39 \pm 3.68 ^b	85.83 \pm 32.81 ^b	671.43 \pm 49.31 ^b	49.86 \pm 4.44 ^b
H	4.34 \pm 1.87 ^a	19.40 \pm 2.91 ^b	2.56 \pm 5.11 ^b	14.93 \pm 2.89 ^b	72.95 \pm 20.26 ^b	734.41 \pm 43.19 ^b	49.43 \pm 3.12 ^b
Groups	LysoPC (17:0/0:0)	LysoPC [20:2(11Z,14Z)/0:0]	LysoPE (0:0/20:0)	LysoPC [18:1(11Z)/0:0]	LysoPC [20:3(5Z,8Z,11Z)/0:0]	LysoPC (16:0/0:0)	
C	180.88 \pm 21.71 ^d	32.40 \pm 2.79 ^d	17.29 \pm 9.65 ^d	329.65 \pm 22.54 ^d	14.99 \pm 6.51	389.56 \pm 30.27	
M	148.41 \pm 24.36 ^b	18.99 \pm 3.35 ^b	5.31 \pm 8.77 ^b	373.64 \pm 30.56 ^b	13.09 \pm 14.03	409.49 \pm 34.57	
H	127.57 \pm 17.42 ^{bc}	18.71 \pm 2.91 ^b	3.27 \pm 7.23 ^b	457.43 \pm 36.45 ^{bd}	46.65 \pm 18.74 ^{bd}	443.44 \pm 31.41 ^{bc}	
Groups	LysoPC [18:2(9Z,12Z)/0:0]	LysoPC [20:4(5Z,8Z,11Z,14Z)/0:0]	LysoPC [22:6(4Z,7Z,10Z,13Z,16Z,19Z)/0:0]	LysoPC [16:1(9Z)/0:0]	LysoPC [18:3(6Z,9Z,12Z)/0:0]	LysoPC (14:0/0:0)	
C	359.01 \pm 38.72	369.88 \pm 30.86	254.88 \pm 18.81	36.49 \pm 5.22	6.46 \pm 2.49	29.08 \pm 3.55 ^d	
M	389.11 \pm 18.13	454.28 \pm 45.03 ^b	267.34 \pm 24.39	35.33 \pm 6.22	8.23 \pm 2.11	21.13 \pm 3.40 ^b	
H	491.28 \pm 32.61 ^{bd}	494.82 \pm 43.44 ^{bc}	225.10 \pm 27.92 ^{bd}	55.71 \pm 12.16 ^{bd}	13.56 \pm 3.32 ^{bd}	28.67 \pm 4.64 ^d	
Groups	Linoalaidylcarnitine	21-Hydroxypregnenolone	Tetracosahexanoic acid	Cervonoyl ethanamide	Indoleacrylic acid	Creatine	
C	20.64 \pm 6.07	14.74 \pm 7.95	11.22 \pm 4.63	44.66 \pm 10.08 ^d	108.38 \pm 5.45	19.91 \pm 2.32	
M	15.32 \pm 4.12	10.83 \pm 6.04	9.29 \pm 10.27	12.50 \pm 10.78 ^b	93.05 \pm 14.22	18.99 \pm 2.73	
H	7.64 \pm 1.65 ^{bd}	3.37 \pm 1.94 ^{bd}	2.74 \pm 1.02 ^{bc}	3.81 \pm 3.32 ^b	86.48 \pm 6.73 ^b	14.33 \pm 1.54 ^{bd}	

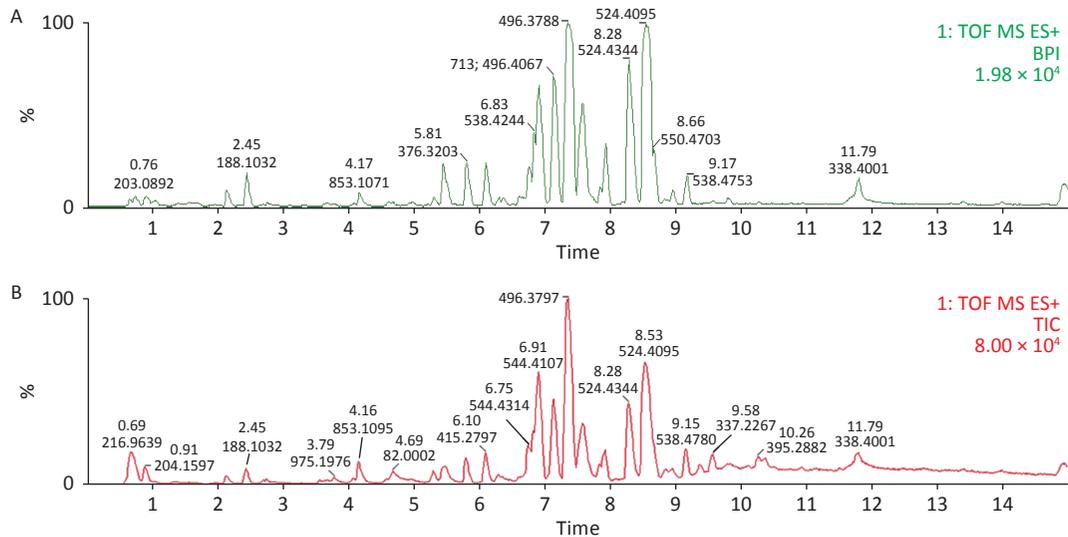
Note. ^a $P < 0.05$ compared to group C. ^b $P < 0.01$ compared to group C. ^c $P < 0.05$ compared to group M. ^d $P < 0.01$ compared to group M. C: Control group, 0 mg/kg; M: Low-dose group, 300 mg/kg; H: High-dose group, 600 mg/kg. DEHP, di (2-ethylhexyl) phthalate; ESI, electrospray ionization.



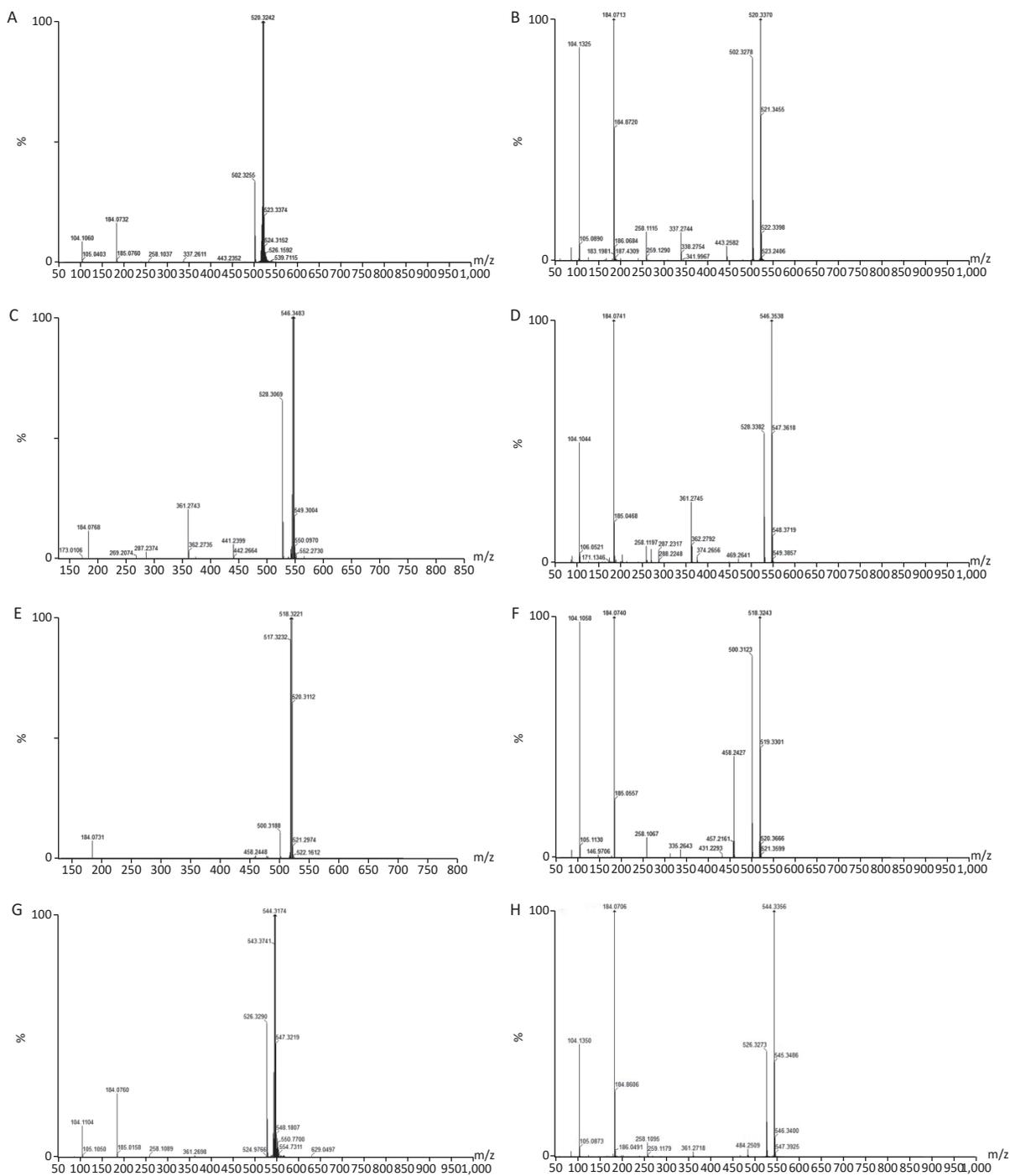
Supplementary Figure S1. (A) Long-term DEHP exposure induced changes in rats' body weight (BW) at each time point. (B) The DEHP exposure levels in male rats' fat and serum at 6 months (means \pm SD, $\mu\text{g/g}$). (C) Long-term DEHP exposure induced alterations of organ/body weight ratio in male rats' liver at 6 month. (D) Altered mRNA expression of liver UDPGT, D1, and CYP2B1 revealed by real-time quantitative PCR. Control: Control group, 0 mg/(kg-day); Low: Low-dose DEHP group, 300 mg/(kg-day); High: High-dose DEHP group, 600 mg/(kg-day). Each data point represents mean \pm standard deviation (SD). * $P < 0.05$, ** $P < 0.01$ compared to the control group. Abbreviations: DEHP, di-(2-ethylhexyl) phthalate. UDPGT, Uridine diphosphate glucuronic acid transferase; CYP2B1, Cytochrome P450 2B1; D1, Cyclin D1.



Supplementary Figure S2. Long-term DEHP exposure altered histopathology in livers of male rats at 6 months. (A) Control group, 0 mg/(kg-day); (B) Low-dose DEHP group, 300 mg/(kg-day); (C) High-dose DEHP group, 600 mg/(kg-day). HE stain magnification, 200 \times . Yellow arrow: fat vacuoles; Blue arrow: inflammatory cell infiltration; Red arrow: hepatocellular injury. DEHP, di-(2-ethylhexyl) phthalate.



Supplementary Figure S3. Representative positive mode BPI and TIC chromatograms of serum from the control (A) and high-dose DEHP (B) groups at month 6 using UPLC/ESI-Q-TOF/MS. BPI, base peak intensity; TIC, total ions chromatogram; ES+, positive ion mode. DEHP, di-(2-ethylhexyl) phthalate. Control group, 0 mg/(kg-day); High-dose DEHP group, 600 mg/(kg-day).



Supplementary Figure S4. Chemical structure and mass fragment information of representative serum biomarkers identified in this study with different collision energy (ev). (A), LysoPC [18:2(9Z, 12Z)/0:0] (25ev). (B), The mass spectra of LysoPC [18:2(9Z, 12Z)/0:0] from the authentic standard (25ev). (C), LysoPC [20:3(5Z, 8Z, 11Z)/0:0] (20ev). (D), The mass spectra of LysoPC [20:3(5Z, 8Z, 11Z)/0:0] from the authentic standard (25ev). (E), LysoPC [18:3(6Z, 9Z, 12Z)/0:0] (10ev). (F), The mass spectra of LysoPC [18:3(6Z, 9Z, 12Z)/0:0] from the authentic standard (15ev). (G), LysoPC [20:4(5Z, 8Z, 11Z, 14Z)/0:0] (15ev). (H), The mass spectra of [20:4(5Z, 8Z, 11Z, 14Z)/0:0] from the authentic standard (20ev).