Supplementary Information (SI 1) for:

Time-trends in human urinary concentrations of phthalates and substitutes DEHT and DINCH in Asian and North American countries (2009–2019)

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Table of Contents

S1. Supplementary Tables 4
S2. Supplementary Figures 17
S3. Additional information 26
S3.1. Urinary concentration units 26
S3.2. Correction of censored data 26
S3.3. Impact of the gender, area, and sample type on the time-trends 26
S3.4. Geographic comparisons 27
References 28

List of Supplementary Tables

Table S 1: literature search on the Web of Science, research keywords and exclusion criteria, and summary of results 4
Table S 2: list of abbreviation/s and definition/s of the parent substances and their metabolite/s found in the literature for phthalates and replacing plasticizers 6
Table S 3: number of central values (priority for median, followed by geometric mean) of unadjusted phthalate urinary concentrations per metabolite and country/region in adults, included in the "PhthaLit" database 9
Table S 4: number of central values (priority for median, followed by geometric mean) of unadjusted phthalate urinary concentrations per metabolite and country/region in children, included in the "PhthaLit" database 11
Table S 5: studies that shared a given Study ID number in the database (data for non-European countries) 12
Table S 6: studies that shared a given Study ID number in the database (data for European countries) 14

List of Supplementary Figures

Figure S 1. Number of measured (>LOD/LOQ, green) and censored (<LOD/LOQ, orange) central values per measured substance in adults, compiled in the "PhthaLit" database 17
Figure S 2: time-trend in the urinary concentrations of 5cx-MEPP (DEHP metabolite, µg/L) in Chinese adults (panel a); available data for 5oxo-MEHP (DEHP metabolite) in Chinese adults (panel b) 17
Figure S 3: time-trends in the urinary concentrations (µg/L) of the DEHP metabolite 5OH-MEHP in Chinese children (panel a) and Korean adults (panel b) 18
Figure S 4: time-trends in the urinary concentrations (µg/L) of: MMP (DMP metabolite) in Chinese children (panel a); MBzP (BBP metabolite) in Chinese children (panel b) and in Taiwanese children (panel c) 18
Figure S 5: time-trends in the urinary concentrations (µg/L) of MiBP (DiBP metabolite) and MEP (DEP metabolite) in Chinese adults (panels a and b, respectively) 19

Figure S 6: time-trends in the urinary concentrations (µg/L) of: MnBP (DnBP metabolite) and MiBP (DiBP metabolite) in US children (panels a and b, respectively); MBzP (BBP metabolite) in Canadian adults (panel c) 19
Figure S 7: time-trends in the urinary concentrations (µg/L) of MCPP in adults from Canada (panel a) and China (panel b) 20
Figure S 8: time-trends for MnBP in Chinese children: a) including all data; b) per sample type (spot urine) 20
Figure S 9: significant time-trends for MnBP in Chinese children per gender (a, both genders; b, girls; c, boys) 21
Figure S 10: significant time-trends for MnBP in Chinese children per area (a, mixed areas; b, suburban; c, urban) 21
Figure S 11: time-trends for 5OH-MEHP in Chinese children: a) including all data; b) for data measured in spot urine; c) for data measured in morning urine 22
Figure S 12: significant time-trends for 5OH-MEHP in Chinese children per gender (a, both genders; b, girls; c, boys) 23
Figure S 13: significant time-trends for 5OH-MEHP in Chinese children per area (a, mixed areas; b, suburban; c, urban) 23
Figure S 14: boxplots of urinary concentrations (µg/L) of low-weight phthalates per continent and period (2009–2014 vs 2015–2019) in adults and children, for: MMP (a), MEP (b), MiBP (c), MBzP (d), and MnBP (e) 25
Figure S 15: boxplots of urinary concentrations (µg/L) per continent and period (2009–2014 vs 2015–2019) in adults and children, for: 5OH-MEHP (a), and MCPP (b). 25

S1. Supplementary Tables

Table S 1: literature search on the Web of Science, research keywords and exclusion criteria, and summary of results

<table>
<tr><th rowspan="2">Research keywords</th><th rowspan="2">Date</th><th colspan="2">Screening of results[a]</th><th colspan="3">Number of publications pre-selected for data compilation</th><th rowspan="2">Number of publications used in data compilation and analysis</th></tr>
<tr><th>Number of results</th><th>Direct exclusion criteria[a]</th><th>Total</th><th>After elimination of duplicates</th><th>Further exclusion criteria for pre-selected publications[b]</th></tr>
<tr><td>TOPIC: phthalate or phthalates or plasticizer or plasticizers
& TITLE: trends or trend</td><td>31/10/19</td><td>50</td><td rowspan="8">• Median sampling year earlier than 2009

• Data not representative of the general population (e.g. occupational exposure)

• Specific physiological stages: pregnancy, breastfeeding</td><td>7</td><td rowspan="7">131</td><td rowspan="8">Sampling year:
• Unclear sampling year (i.e. not shown, N=6)
• Very long sampling campaign (>4 y; N=2)

Data which may not be representative of general population in a country:
• Hotspot region (N=4)
• Subjects undergoing infertility study/treatment (N=14)
• Subjects with chronic health problems (N=3)
• Publications with low sample sizes were not prioritized. These publications were directly excluded if N<20 (N=6)

Other reasons:
• The HBM data shown were already compiled from other publications (N=16)
• No quantitative data of interest for our study (N=6)
• Neither median nor geometric mean values shown (N=3)
• Use of plastics for sample collection (N=2)
• Matrix, i.e. serum instead of urine (N=2)
• Data for infants (N=1)</td><td>88</td></tr>
<tr><td>TOPIC: DEHP or (ethylhexyl and phthalate) or (ethylhexylphthalate) or (ethyl and hexyl and phthalate)
& TOPIC: (human or dust) and concentration
& TOPIC: trend</td><td>16/01/20</td><td>87</td><td>15</td></tr>
<tr><td>TOPIC: phthalate and concentration and human and urine
YEAR: from 2009 to 2020</td><td>28/01/20</td><td>440</td><td>93</td></tr>
<tr><td>TOPIC: phthalate and concentration and human and urine
YEAR: from 2020 to 2021</td><td>22/01/21</td><td>67</td><td>16</td></tr>
<tr><td>TOPIC: phthalate or phthalates or plasticizer or plasticizers
& TOPIC: human and (urine or urinary or plasma or blood or serum)
YEAR: from 2019 to 2020</td><td>27/04/20 and 12/10/20</td><td>391 results screened</td><td>43</td></tr>
<tr><td>TOPIC: terephthalate or DEHT or DEHTP or DOTP or DINCH or MINCH or (cyclohexane and (dicarboxylic or dicarboxylate)) or cyclohexanedicarboxylic or cyclohexanedicarboxylate or (adipate and plasticizer)
& TOPIC: human and (urine or urinary or plasma or blood or serum)</td><td>05/10/20</td><td>245 results since 2009</td><td>25</td></tr>
<tr><td>Other sources (mainly citations)</td><td>2020</td><td></td><td colspan="2">48</td><td>26</td></tr>
<tr><td>TOPIC: phthalate* or terephthalate* or deht* or dotp or dinch or (cyclohexanedicarboxylic or (cyclohexane and dicarboxylate)) or plasticizer*</td><td>03/06/21[c]</td><td>434 results, of which 224 results since</td><td colspan="2">9</td><td>At this stage of our study, all exclusion criteria were considered and priority data were compiled [c]</td><td>9</td></tr>
</table>

AND TOPIC: urin* YEAR: 2020 to 2021		Sep. 2020 were screened					
Total				256	188	65	123

[a] Title, abstract, and, if needed, material and methods were screened

[b] In the table, we show the number of publications excluded based on these criteria. Moreover, for publications included in data compilation, some groups of subjects were also excluded based on the same criteria (e.g. if obese and control groups were analyzed separately, we only compiled data for the control group)

[c] At this stage (in June 2021), all exclusion criteria were considered during the screening of results. Additionally, in this last research data which were not a priority for our study (e.g. data which were not reported unadjusted, or data for non-priority age groups for our study such as seniors or younger children) were not included in the database. At this stage, priority data included relevant data in Asian and North American countries, and recent data (since 2015) in other continents.

Table S 2: list of abbreviation/s and definition/s of the parent substances and their metabolite/s found in the literature for phthalates and replacing plasticizers

Parent substance		**Metabolite**	
Abbreviation/s	**Definition/s**	**Abbreviation/s**	**Definition/s**
Low molecular weight phthalates			
DMP	Dimethyl phthalate	**MMP**	Mono-methyl phthalate
DEP	Diethyl phthalate	**MEP**	Mono-ethyl phthalate
DiPrP; DIPrP	Diisopropyl phthalate	**MiPrP**	Mono-isopropyl phthalate
DnPrP; DPrP	Dipropyl phthalate; Di-n-propyl phthalate	**MnPrP**	Mono-n-propyl phthalate
DiBP; DIBP	Di-isobutyl phthalate	**MiBP**	Mono-isobutyl phthalate; Mono-2-isobutyl phthalate
		OH-MiBP; 2OH-MiBP; MHiBP	2OH-Mono-isobutylphthalate; mono-hydroxy-iso-butyl phthalate; mono-2-methyl-2-hydroxypropyl phthalate.
DnBP; DBP	Dibutyl phthalate; di-n-butyl phthalate	[a] **MnBP**; MBP	Mono-n-butyl phthalate; monobutyl phthalate
		OH-MnBP; 3OH-MnBP; MHBP	3OH-Mono-n-butyl phthalate; mono-hydroxy-n-butyl phthalate; Mono(4-hydroxybutyl) phthalate (1)
BBP; BBzP	Benzyl butyl phthalate; butyl benzyl phthalate	**MBzP**	Mono-benzyl phthalate
DCHP; DcHP	Dicyclohexyl phtalate; 1,2-Benzenedicarboxylic acid, 1,2-dicyclohexyl ester	**MCHP**; McHP	Mono-cyclohexyl phtalate
DiPeP; DiPP	Di-isopentyl phthalate	**MiPeP**; MiPP	Mono-isopentyl phthalate
DnPeP; DnPP; DPeP	Di-n-pentylphthalate; Dipentyl phthalate	**MHPeP**	Mono-4-hydroxypentyl phthalate
		MnPeP; MPeP	Mono-n-pentyl phthalate
DHxP; DHP; DnHP	Dihexyl phthalate; 1,2-Benzenedicarboxylic acid, 1,2-dihexyl ester; Di-n-hexyl phthalate	**MHxP**; MnHP	Monohexyl phthalate; Mono-n-hexyl phthalate
		OH-MHxP	Mono-(5-hydroxyhexyl) phthalate
		cx-MPeP	Mono-(5-carboxypentyl) phthalate
High molecular weight phthalates			
DEHP	Di(2-ethylhexyl) phthalate; bis(2-ethylhexyl) phthalate	**5cx-MEPP**; MECPP; cx-MEPP	Mono(2-ethyl-5-carboxy-pentyl) phthalate; Mono-ethyl-carboxy-pentyl phthalate
		5OH-MEHP; MEHHP; OH-MEHP	Mono(2-ethyl-5-hydroxy-hexyl) phthalate; Mono-ethyl-hydroxy-hexyl phthalate
		5oxo-MEHP; MEOHP; oxo-MEHP	Mono(2-ethyl-5-oxo-hexyl) phthalate; Mono-ethyl-oxo-hexyl phthalate
		MCMHP; 2cx-MMHP	Mono-carboxy-methyl-hexyl phthalate; Mono-2-carboxymethyl-hexyl phthalate
		MEHP	Mono(2-ethylhexyl) phthalate; Mono-ethyl-hexyl phthalate
DiHpP	Diisoheptyl phthalate	**MiHpP**	Monoisoheptyl phthalate
		MOHpP	Mono-oxoheptylphthalate
		cx-MHxP; MCHxP	Mono-(6-carboxyhexyl) phthalate; Monocarboxyhexyl phthalate
DnHpP; DHpP	Di-n-heptyl phthalate	**MHHpP**; OH-MHpP	Monohydroxyheptyl phthalate; Mono-(6-hydroxyheptyl) phthalate
		MnHpP; MHpP	Mono-n-heptyl phthalate; Monoheptyl phthalate; mono-2-heptyl phthalate
DOP; DnOP		**MOP**; MnOP	Mono-n-octyl phtalate; Monooctyl phthalate

	Dioctyl phthalate; 1,2-Benzenedicarboxylic acid, 1,2-dioctyl ester; Di-n-octyl phtalate	**MCHpP**; mCHpP	Mono(7-carboxyheptyl) phthalate; Mono-carboxy-n-heptyl phthalate
[b] **DPHP**	Bis(2-propylheptyl) phthalate; 1,2-Benzenedicarboxylic acid, 1,2-bis(2-propylheptyl) ester	**cx-MPHP**; cx-MPHxP	mono (2-propyl-6-carboxyhexyl)-phthalate; mono (propyl-6-carboxyhexyl)-phthalate
		OH-MPHP	mono(2-propyl-6-hydroxyheptyl)-phthalate; mono(propyl-6-hydroxyheptyl)-phthalate; 6-Hydroxy Monopropylheptylphthalate;
		oxo-MPHP	mono (2-propyl-6-oxo-heptyl)-phthalate; mono (propyl-6-oxo-heptyl)-phthalate
		MPHP	monopropylpheptyl phthalate; mono(2-propylheptyl) phthalate
DINP; DiNP	Diisononyl phtalate; 1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester	**cx-MINP**; cx-MiNP; MCiOP; MCOP	Mono-carboxy-octyl phthalate; Mono-carboxy-isooctyl phthalate; Mono(6-carboxy-2-methylheptyl) phthalate (2-4); 7-Carboxy-(mono-methyl-heptyl) phthalate (5, 6); Mono-(4-methyl-7-carboxyheptyl)phthalate (7)
		MINP; MiNP; MNP	Mono-isononyl phthalate
		OH-MINP; OH-MiNP; MHiNP	Mono-hydroxy-isononyl phthalate (3, 4); 7-OH-(Mono-methyl-octyl) phthalate (5)
		oxo-MINP; oxo-MiNP; MOiNP; MONP	Mono-oxo-isononyl phthalate (3, 4); 7-Oxo-(Mono-methyl-octyl) phthalate (5)
[b] **DIDP**; DiDP	Diisodecyl phthalate; 1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester	**MIDP**; MiDP	Mono-isodecyl phthalate (3, 8); Mono(8-methyl-1-nonyl) phthalate (9)
		cx-MIDP; cx-MiDP; MCNP; MCINP; MCiNP	Mono(2,7-methyl-7-carboxy-heptyl) phthalate (5); mono-carboxy-isononyl phthalate; Monocarboxynonyl phthalate (2, 10); Mono-(9-carboxynonyl) phthalate (3)
		OH-MIDP; OH-MiDP; MHiDP	Mono-hydroxy-isodecyl phthalate (10); 6-OH-mono-propylheptyl phthalate; 6-hydroxypropylheptyl phthalate (5, 11); Mono-(9-hydroxydecyl) phthalate (3)
		oxo-MIDP; oxo-MiDP; MOiDP	Mono-oxo-isodecyl phthalate (included under this definition as a DIDP metabolite by Health Canada and Schutze et al. (4, 10); 6-oxo-mono-propylheptyl phthalate (5); Mono-(9-oxodecyl) phthalate (3);
Several parental phthalates (including DnBP, DnPeP, DnOP, DiNP, DiDP; (5, 12)		**MCPP**; 3cx-MPP	Mono-3-carboxypropyl phtalate; 3-carboxyl-mono-propyl phthalate
Phthalate replacements (substitutes)			
DINCH (Hexamoll® DINCH)	1,2-Cyclohexanedicarboxylic acid, 1,2-diisononyl ester; di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate;	**cx-MINCH**; MCOCH	Cyclohexane-1,2-dicarboxylic acid-mono (carboxy-isooctyl) ester
		MINCH	cyclohexane-1,2-dicarboxylic acid-mono(isononyl) ester
		OH-MINCH; MHINCH; MHNCH	Cyclohexane-1,2-dicarboxylic acid-mono (hydroxyl-iso-nonyl) ester (13-15)
		oxo-MINCH; MOiNCH; MONCH	Cyclohexane-1,2-dicarboxylic acid-mono (oxo-isononyl) ester (13-15)
		CHDA	Cyclohexane-1,2-dicarboxylic acid
DEHT; DEHTP; DOTP	Bis(2-ethylhexyl) terephthalate; di(2-ethylhexyl) terephthalate;	**2cx-MMHTP**	1-mono-(2-carboxyl-methyl-hexyl) benzene-1,4-dicarboxylate; Mono-(2-carboxyl-methyl-hexyl) terephthalate

	1,4-Benzenedicarboxylic acid, 1,4-bis(2-ethylhexyl) ester; Dioctyl terephthalate	**5cx-MEPTP**; MECPTP	Mono-2-ethyl-5-carboxypentyl terephthalate; 1-mono-(2-ethyl-5-carboxyl-pentyl) benzene-1,4-dicarboxylate;
		5OH-MEHTP; MEHHTP	Mono-2-ethyl-5-hydroxyhexyl terephthalate; 1-Mono-(2-ethyl-5-hydroxy-hexyl) benzene-1,4-dicarboxylate;
		5oxo-MEHTP	1-mono-(2-ethyl-5-oxo-hexyl) benzene-1,4-dicarboxylate; Mono-(2-ethyl-5-oxo-hexyl) terephthalate
		MEHTP	Mono(2-ethylhexyl) terephthalate
[c] **DEHA**	Di(2-ethylhexyl)adipate; Di-octyl adipate	**MEHA**	Mono-2-ethylhexyl adipate
		MEHHA	Mono-2-ethylhydroxyhexyl adipate
		MEOHA; oxo-MEHA	Mono(2-ethyl-5-oxohexyl) adipate
[c] **DnBA**	Di-n-butyl adipate; Hexanedioic acid, dibutyl ester	**3cx-MnPrA**	3-carboxy-mono-n-propyl adipate
		3OH-MnBA	3-hydroxy-mono-n-butyl adipate
		MnBA	mono-n-butyl adipate
[c] **TCEPho**	Tris(2-chloroethyl)phosphate	**DCEPho**; BCEPho	Di(2-chloroethyl)phosphate; bis(chloroethyl) phosphate; bis(2-chloroethyl) phosphate
[c] **TnBPho**	Tri-n-butyl phosphate	**DnBPho**; DBPho	Di-n-butyl phosphate; dibutyl phosphate
[c] **TCPho**	Tricresyl phosphate-isomers	**DmCPho**	Di-m-cresyl phosphate
		DoCPho	Di-o-cresyl phosphate
		DpCPho	Di-p-cresyl phosphate

In the table, references are given for definitions that were relatively heterogeneous between publications

[a] MnBP can also be formed from BBP (16)

[b] DIDP and DPHP metabolites may not be clearly distinguished through high performance liquid chromatography coupled to tandem mass spectrometry (HPLC–MS/MS) (5). For these substances we used the same classification (i.e. classification as either DIDP or DPHP metabolites) that was shown in each publication

[c] Our literature research did not focus on adipates or phosphates, for which data were found under the general keyword "plasticizers". Additional data exist in the literature for these substances, notably for phosphates.

Table S 3: number of central values (priority for median, followed by geometric mean) of unadjusted phthalate urinary concentrations per metabolite and country/region in adults, included in the "PhthaLit" database

Measured.subst.abbreviation	China	India	Israel	Japan	Korea	Malaysia	Saudi Arabia	Taiwan	Vietnam	Austria	Belgium	Czech Republic	Denmark	Finland	France	Germany	Hungary	Italy	Norway	Slovakia	Slovenia	Spain	Sweden	United Kingdo	Canada	US	Australia	All countries
MMP	18	1	0	1	2	1	2	3	1	0	1	1	3	0	1	4	1	0	1	2	0	0	0	0	3	2	1	49
MEP	19	1	0	1	2	1	2	3	1	1	3	2	5	1	1	5	1	2	3	3	1	1	2	1	3	4	1	77
MiBP	18	1	1	1	3	1	2	3	1	1	3	1	5	1	1	5	0	0	3	1	1	1	0	1	3	4	1	70
MnBP	19	1	1	1	6	1	2	3	1	1	3	1	5	1	1	5	0	2	3	2	1	1	1	1	3	4	1	78
OH-MnBP	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	4	0	0	0	0	0	0	0	0	1	2	0	10
MBzP	17	1	1	1	5	1	2	3	1	1	3	2	5	1	1	5	1	2	3	1	1	1	2	1	3	4	1	77
MCHP	6	1	0	1	3	1	2	0	1	1	0	1	3	1	1	4	1	0	0	2	0	0	0	0	3	1	1	34
MnPeP	1	0	0	0	2	0	1	0	0	1	0	0	3	0	0	4	0	0	0	0	0	0	0	0	0	0	0	12
5cx-MEPP	12	1	1	1	4	1	2	3	1	1	1	1	4	1	0	4	0	0	2	1	0	0	2	0	2	11	1	57
5OH-MEHP	19	1	1	1	9	1	2	3	1	1	3	2	4	1	1	4	1	2	3	2	1	1	2	1	3	8	1	79
5oxo-MEHP	19	1	1	1	9	1	2	3	1	1	3	2	4	1	1	4	1	0	3	2	1	1	2	1	3	4	1	73
MCMHP	8	1	1	1	2	1	2	2	1	0	0	0	3	0	0	0	0	0	1	0	0	0	0	0	1	0	0	24
MEHP	19	1	1	1	6	1	2	3	1	1	3	2	4	1	1	4	1	2	3	3	1	1	2	1	3	4	2	74
MOP	4	1	0	1	2	1	2	0	1	1	0	0	4	1	1	4	0	0	0	1	0	0	0	0	3	1	3	31
cx-MINP	0	0	1	0	2	0	0	0	0	0	0	1	4	1	0	4	0	0	2	0	0	1	2	0	1	7	1	27
MINP	7	1	0	1	2	1	2	3	1	1	0	0	4	1	1	0	0	0	0	2	0	0	0	0	3	4	2	36
OH-MINP	0	0	1	0	1	0	0	0	0	0	0	1	4	0	0	4	0	0	2	0	0	0	2	0	1	0	0	16
oxo-MINP	0	0	1	0	0	0	0	0	0	0	0	1	4	0	0	4	0	0	2	0	0	0	2	0	1	1	0	16
cx-MIDP	0	0	0	0	1	0	0	0	0	0	0	0	3	1	0	4	0	0	0	0	0	0	0	0	1	4	1	15
MIDP	0	0	0	0	2	0	2	1	0	1	0	0	4	0	0	0	0	0	0	0	0	0	0	0	1	0	3	14
MCPP	7	1	0	1	3	1	2	0	1	1	0	1	4	0	1	4	0	0	0	0	0	0	0	0	3	4	1	35
cx-MINCH	0	0	0	0	1	0	0	0	0	0	0	0	3	0	0	7	0	0	1	0	0	0	0	0	0	4	0	16
OH-MINCH	0	0	0	0	1	0	0	0	0	0	0	0	3	0	0	7	0	0	2	0	0	0	0	0	1	6	0	20
oxo-MINCH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	1	0	0	0	0	0	1	3	0	12

5cx-MEPTP	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	6	0	0	0	0	0	0	0	0	0	5	0	14
5OH-MEHTP	0	0	0	0	1	0	0	0	0	0	0	0	3	0	0	6	0	0	0	0	0	0	0	0	0	5	0	15
All metabolites	198	14	11	14	82	14	36	33	14	14	23	22	133	14	12	153	7	10	37	22	7	8	19	7	50	101	22	1105[a]

Main matrix (white and blue scale): only countries for which the number of central values (n) was >= 5, and metabolites for which n was >= 10 are shown

Totals (white and grey scale): including all countries and metabolites in the database

The abbreviations of all metabolites are defined in Table S 2

a More data were compiled later. The final version of the “PhthaLit” database, used in the analyses shown in the main manuscript, contains n = 1208 unadjusted central values for adults

Table S 4: number of central values (priority for median, followed by geometric mean) of unadjusted phthalate urinary concentrations per metabolite and country/region in children, included in the "PhthaLit" database

Measured.subst.abbreviation	China	Egypt	Korea	Saudi Arabia	Taiwan	Austria	Belgium	Czech Republic	Denmark	France	Germany	Greece	Hungary	Norway	Poland	Portugal	Slovakia	Slovenia	Spain	Sweden	United Kingdom	Canada	US	Mexico	Brazil	All countries
MMP	12	0	0	1	6	0	0	1	0	1	2	0	1	0	1	1	2	0	0	0	0	2	2	0	1	33
MEP	14	2	0	1	6	2	2	1	3	1	4	1	1	1	2	2	2	1	1	2	1	2	5	3	1	66
MiBP	10	2	0	1	5	2	2	2	3	1	4	1	0	1	2	2	1	1	1	0	1	2	5	3	1	58
MnBP	14	2	1	1	6	2	2	2	3	1	4	1	0	1	2	2	1	1	1	1	1	2	5	3	1	65
MBzP	9	2	1	1	6	2	2	3	3	1	4	1	1	1	2	2	1	1	1	2	1	2	5	3	1	63
MCHP	5	0	0	1	0	2	0	1	0	1	2	0	1	0	1	1	2	0	0	0	0	2	1	0	1	21
5cx-MEPP	8	2	1	1	2	2	0	0	2	0	2	0	0	1	1	1	1	0	0	2	0	1	5	3	1	36
5OH-MEHP	14	2	1	1	6	2	2	3	2	1	3	1	1	1	1	1	2	1	1	2	1	2	5	3	1	62
5oxo-MEHP	14	2	1	1	6	2	2	3	2	1	3	1	1	1	1	1	2	1	1	2	1	2	5	3	1	62
MEHP	14	2	0	1	6	2	2	3	2	1	2	1	1	1	1	1	2	1	1	2	1	2	5	3	1	60
MOP	4	0	0	1	0	2	0	0	1	1	2	0	0	0	1	1	1	0	0	0	0	2	1	0	1	18
cx-MINP	1	2	1	0	0	0	0	0	1	0	2	0	0	1	1	1	0	0	1	2	0	1	5	0	1	20
MINP	3	0	0	1	4	2	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	2	5	0	1	21
oxo-MINP	0	0	0	0	0	0	0	0	1	0	3	0	0	1	1	1	0	0	0	2	0	1	2	0	0	12
cx-MIDP	0	2	1	0	0	0	0	0	0	0	2	0	0	0	1	1	0	0	0	1	0	1	5	0	1	15
MCPP	1	2	1	1	0	2	0	0	1	1	2	0	0	0	1	1	0	0	0	0	0	2	5	3	1	24
All metabolites	134	22	8	18	53	28	14	19	27	12	72	7	7	11	25	29	18	7	8	23	7	37	86	27	24	750[a]

Main matrix (white and blue scale): only countries for which the number of central values (n) was >= 5, and metabolites for which n was >= 10 are shown

Totals (white and grey scale): including all countries and metabolites in the database

The abbreviations of all metabolites are defined in Table S 2

a More data were compiled later. The final version of the "PhthaLit" database, used in the analyses shown in the main manuscript, contains n = 859 unadjusted central values for children

Table S 5: studies that shared a given Study ID number in the database (data for non-European countries)

Study. ID.number	Study.name	Country / region	Specific location	Biomonitoring plan / biobank	Sampling years	Average year	Descript.Population	Age.group.category	N	Gender	Matrix
6	Choi et al., 2017 (26); Park et al., 2019 (27)	South Korea	Several locations in South Korea	Korean National Environmental Health Survey (KoNEHS)	June 2012 - May 2014	2013	Adults (> 19 y; N=6470)	adults	6470	Both	Spot urine
	Park et al., 2016 (28)				2009-2011	2010	Adults (> 19 y; N=6274)	adults	6274		
	Lim S., 2020 (29)				Aug. 2015 - Jul. 2017	2016	Children (6-11 y; N=839)	children	839		
							Teenagers (12-17 y; N=807)	teenagers	807		
							Adults (19-86 y; N=3759)	adults	3759		
29	Lee I. et al., 2019 (23); Kang et al., 2019 (30)	South Korea	Several locations	-	2015–2016	2016	Women (N=459 in Lee et al., 2019; N=441 in Kang et al., 2019; same population in both studies; 20–48 years-old)	adults	450	Female	Spot urine
20	Chen JS et al., 2019 (31)	China	Shanghai, 9 urban and suburban districts/counties	Shanghai Food Consumption Survey (SHFCS)	2012	2012	Adults (N=1663)	adults	1663	Both	Spot urine
	Dong et al., 2018 (32)				Sep. 2012 - Aug. 2014	2013	Boys (8-11 y; N=64)	children	64	Male	
							Girls (8-11 y; N=65)	children	65	Female	
							Teenage boys (12-19 y; N=76)	teenagers	76	Male	
							Teenage girls (12-19 y; N=66)	teenagers	66	Female	
							Men (45-60 y; N=471)	adults	471	Male	
							Women (45-60 y; N=401)	adults	401	Female	
16	Liao et al., 2017, 2018 (33, 34)	China	Shanghai, several areas	China, Children, Homes, Health (CCHH) study	2013-2014	2014	Children (5-10 y; N=434)	children	434	Both	Morning urine

93	Yao et al., 2019, 2020 (24, 35)	China	Shenzhen, eight districts: Guangming, Baoan, Dapeng, Futian, Nanshan, Longhua, Longgang and Pingshan	EHC-PRD study (environment and health in children in the Pearl River Delta, China)	Sep 2016 - Jun 2017	2017	Children (6–8 y, average age 7.8 y; N=1490; 59% boys)	children	1490	Both	Spot urine
97	Huang et al., 2021 (36)	Taiwan	11 cities	Taiwan Environmental Survey for Toxicants (TEST) and National and Nutrition Health Survey in Taiwan (NAHSIT)	May-Dec 2013	2013	Adults (52.7 ± 17.5 y; N=217)	adults	217	Both	Spot urine
	Liao et al., 2021 (37)		20 cities, different areas and regions		May 2013 - Dec 2016	2015	Children (7-11 y; N=336)	children	336	Both	Morning urine
							Adults (>= 18 y; N=1264)	adults	1264	Both	
73	Goodrich et al., 2016 (38)	Mexico	Mexico city	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) birth cohorts	2011-2012	2012	Children and teenagers (8-14 y; N=238)	children	238	Both	Spot urine
	Lewis et al., 2013 (39)				2010	2010	Boys (8-13 y; N=53)	children	53	Male	Spot urine
78	Feng et al., 2020 (40)	Canada	Montreal	Protocol number A01-M14-10B	2009 to 2012	2011	Men (fertile, control) (18-39 y; N=106)	adults	106	Male	Spot urine
	Albert et al., 2018 (41)						Men (fertile, control) (18-41 y; N=117)	adults	117		
35	Tang et al., 2020 (42)	Australia	Queensland	-	Nov 2012-Dec 2013	2013	General population (N=24 pools of 100 individual samples each, 8 pools for average ages < 18 y and 16 pools for average ages > 18 y)	adults	2400	Both	Spot urine
	Gomez-Ramos et al., 2016 (43)					2013					

Table S 6: studies that shared a given Study ID number in the database (data for European countries)

Study.ID	Study.name	Country / region	Specific location	Biomonitoring plan / biobank	Sampling years	Average year	Descript.Population	Age.group.category	N	Gender	Matrix
5	Schoeters et al., 2017 (44); Koppen et al., 2020 (45)	Belgium	Flanders	FlemishEnvironment and Health Study (FLEHS)	2013	2013	Adolescents (14-17 y; N=207 in 2013, FLEHS III)	teenagers	207	Both	Spot urine
					2017-2018	2018	Adolescents (14.77±0.47 y; N=416)	teenagers	416		
2	Schwedler et al., 2020 (13)	Germany	Several	German Environmental Survey of Children and Adolescents (GerES)	Jan 2015 - Jun 2017	2016	Children (6-10 y; N=166)	children	166	Both	Morning urine
	Schwedler et al., 2020 (12)						Children (6-10 y; N=736)	children	736		
	Schwedler et al., 2020. (46)						Children (6-10 y; N=696)	children	696		
3	Schutze et al., 2015 (10)	Germany	Münster	German Environmental Specimen Bank-German Environment Agency (ESB-UBA)	Several campaigns	Average year per campaign	Young adults (university students; 20 to 30 year-old, N=60 per sampling year)	adults	60	Both	24-h urine
	Schmidtkunz et al., 2019 (47)										
	Lessmann et al., 2019 (48)										
	Schutze et al., 2014 (49)										
	Kasper-Sonnenberg et al., 2019 (14)										
	Koch et al., 2017 (5)										
8	Fromme et al., 2013, 2015 (50, 51)	Germany	Bavaria, Berlin, North Rhine-Westfalia	Länderuntersuchungsprogramme, LUPE 3	Nov 2011-May 2012	2012	Children (1.7 to 6.7 y; N=208-663)	children	208-663	Both	Spot urine
	Fromme et al., 2014 (52)						Children (1.8-6.7 y; N=312)		312		

39	Den Hond et al., 2015 (53)	Several		Consortium to Perform Human Biomonitoring on a EuropeanScale (COPHES) and Demonstration of a study to Coordinate and Perform Human Biomonitoringon a European Scale (DEMOCOPHES)	2011 - 2012 (exact dates slightly different per country)	2011 or 2012	Children (5-11 years-old; N=120 approx.) and Mothers (N=120 approx.)	children / adults	Dependent on the age group and country	Both (children) / Female (mothers)	Morning urine
	Koppen et al., 2019 (54)	Belgium				2012					
	Cerna et al., 2015 (55)	Czech Republic				2012					
	Schwedler et al., 2017 (56)	Germany				2011					
	Cullen et al., 2017 (57)	Ireland				2012					
	Runkel et al., 2020 (58)	Slovenia			2011	2011					
	Cutanda et al., 2015 (6)	Spain			Oct. 2011 - Jan. 2012	2012					
	Larsson et al., 2014 (59)	Sweden			Sep. 2011 - Feb. 2012	2012					
	Exley et al., 2015 (60)	United Kingdom			Jan to Apr. 2012	2012					
40	Myridakis et al., 2015 (61)	Greece	Crete	Rhea cohort	March 2009–June 2011_Rhea project	2010	Toddlers (2.3 ± 0.72 y; N=390)	younger children	390	Both	Spot urine
	Myridakis et al., 2016 (62)				2011-2013	2012	Children (4.24 ± 0.24 y; N=500)	children	500		
	Haug et al., 2018 (63)			Early-Life Exposome project (HELIX), Rhea cohort	2014	2014	Children (6.5±0.3 y; N=199)	children	199		Morning urine
		Lithuania		Early-Life Exposome project (HELIX)	2014	2014	Children (6.5±0.5 y; N=204)	children	204		
48	Tranfo et al., 2013 (64)	Italy	Lazio	-	2011	2011	Women (29-47 y; N=83)	adults	83	Female	Spot urine
	Tranfo et al., 2018 (65)		Central Italy		2016	2016	Women (N=111 in 2016)	adults	111		

50	Giovanoulis et al., 2016 (66); Alves et al., 2017 (67)	Norway	Oslo	Advanced Tools for Exposure Assessment and Biomonitoring (A-TEAM) project	Winter 2013-2014_A-TEAM project	2014	Adults (20-66 y; N=61)	adults	61	Both	Spot urine
57	Milošević et al., 2018 (68)	Serbia	Vojvodina region	-	June 2015 to June 2016	2016	Men, normal-weight (18-55 y; N=51)	adults	51	Male	Morning urine
	Milošević et al., 2020 (69)				n.s.	-	Adults, normal-weight (18-50 y; N=100)	adults	100	Both	Morning urine
52	Polanska et al., 2014 (70)	Poland	Łódź	Polish Mother and Child Cohort Study (REPRO_PL)	Unclear, 2010 – 2013 approx.	-	Children (23–28 months; N=165)	younger children	165	Both	Spot urine
	Garí et al., 2019 (71)				2014-2015	2015	Children (7.2±0.23 y; N=250)	children	250		
53	Correia-Sá et al., 2017 (72)	Portugal	Oporto and Aveiro	-	2014-2015	2015	Children and teenagers, normal-weight or underweight (4-18 y; N=39-43)	children	39-43	Both	Morning urine
	Correia-Sá et al., 2018 (73)										
	Lessmann et al., 2017 (74)										

S2. Supplementary Figures

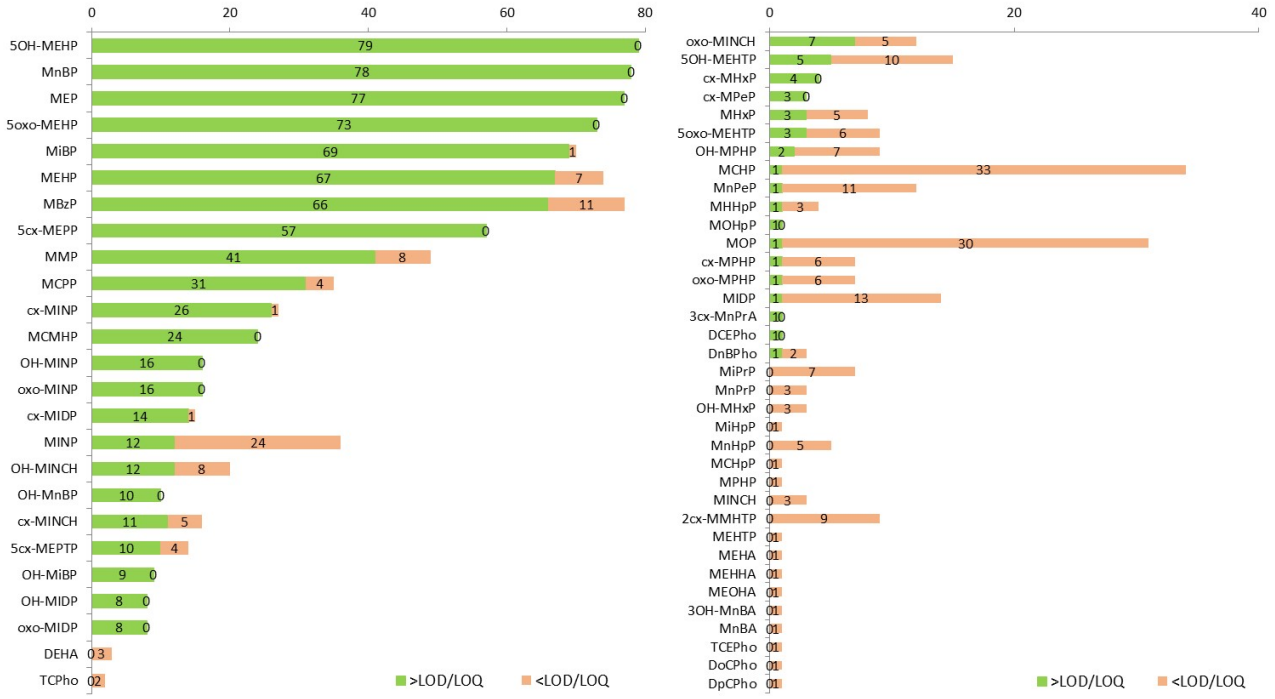


Figure S 1. Number of measured (>LOD/LOQ, green) and censored (<LOD/LOQ, orange) central values per measured substance in adults, compiled in the "PhthaLit" database

LOD: limit of detection; LOQ: limit of quantification.
The metabolites in this Figure are organized from higher to lower number of measured data per substance.
The abbreviations of all metabolites are defined in Table S 2.

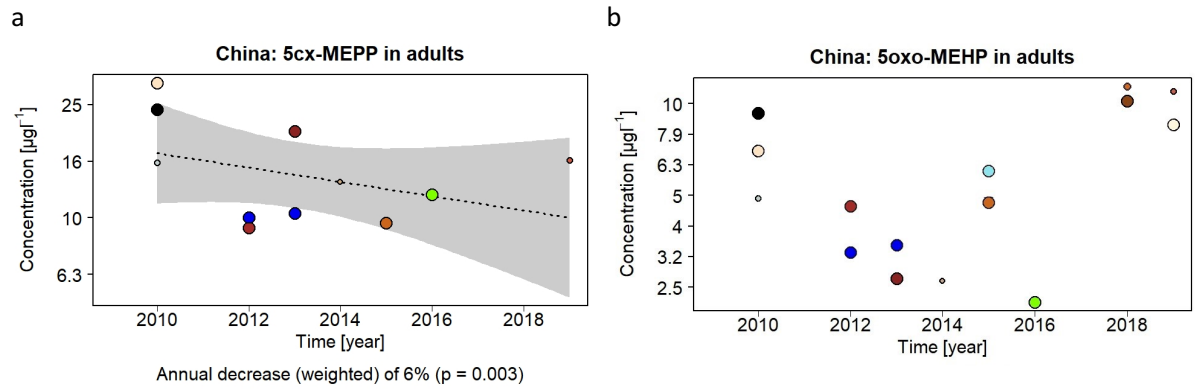


Figure S 2: time-trend in the urinary concentrations of 5cx-MEPP (DEHP metabolite, µg/L) in Chinese adults (panel a); available data for 5oxo-MEHP (DEHP metabolite) in Chinese adults (panel b)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Data from the same data source (Study ID number, see Data traceability in the "PhthaLit" database) are identified by symbols with the same colour in all panels and Figures. Grey area: 90% confidence interval.

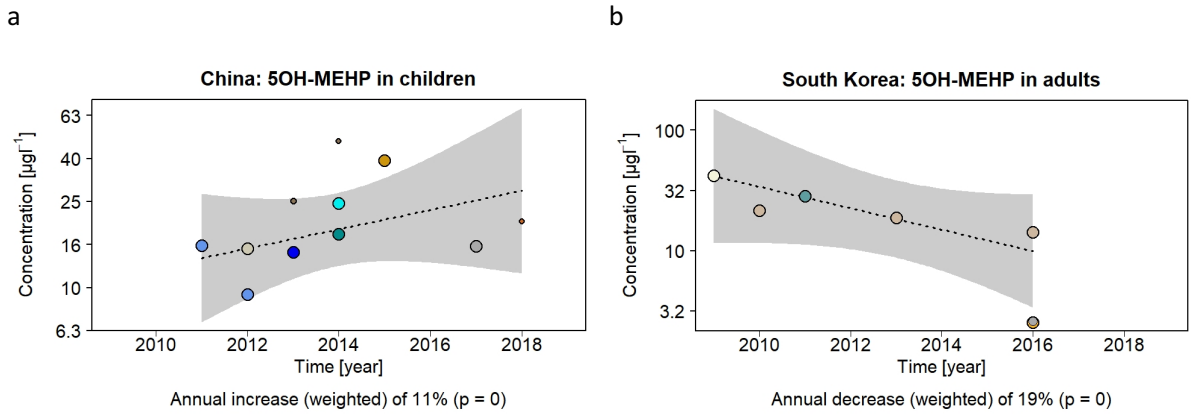


Figure S 3: time-trends in the urinary concentrations (µg/L) of the DEHP metabolite 5OH-MEHP in Chinese children (panel a) and Korean adults (panel b)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Data from the same data source (Study ID number, see Data traceability in the "PhthaLit" database) are identified by symbols with the same colour in all panels and Figures. Grey area: 90% confidence interval. The p-value was < 0.001 for both trends

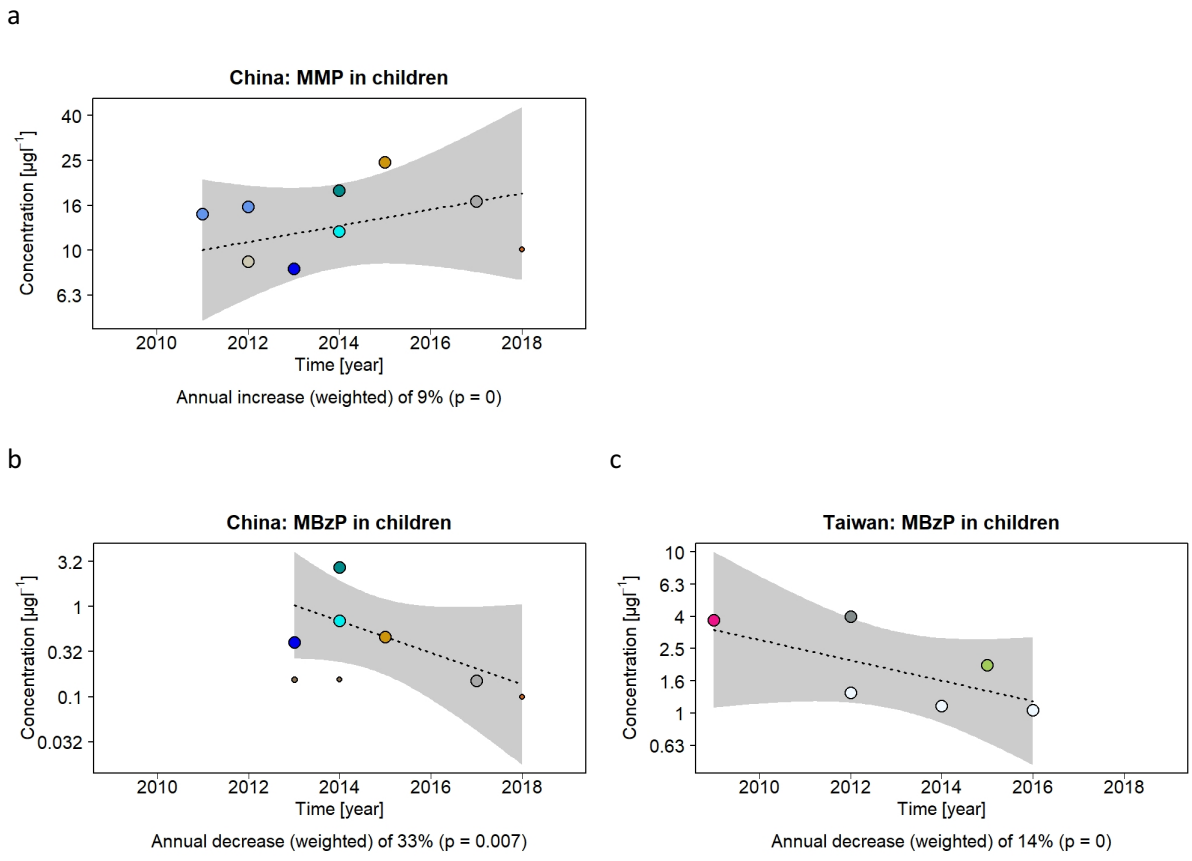


Figure S 4: time-trends in the urinary concentrations (µg/L) of: MMP (DMP metabolite) in Chinese children (panel a); MBzP (BBP metabolite) in Chinese children (panel b) and in Taiwanese children (panel c)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Data from the same data source (Study ID number, see Data traceability in the "PhthaLit" database) are identified by symbols with the same colour in all panels and Figures. Grey area: 90% confidence interval. The p-value was < 0.001 for the trends shown in panels a and c

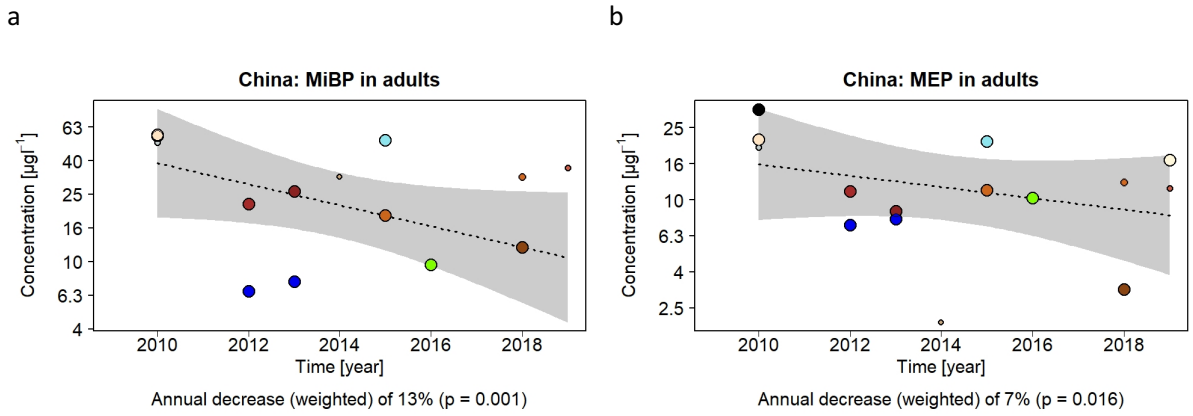


Figure S 5: time-trends in the urinary concentrations (µg/L) of MiBP (DiBP metabolite) and MEP (DEP metabolite) in Chinese adults (panels a and b, respectively)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Data from the same data source (Study ID number, see Data traceability in the "PhthaLit" database) are identified by symbols with the same colour in all panels and Figures. Grey area: 90% confidence interval.

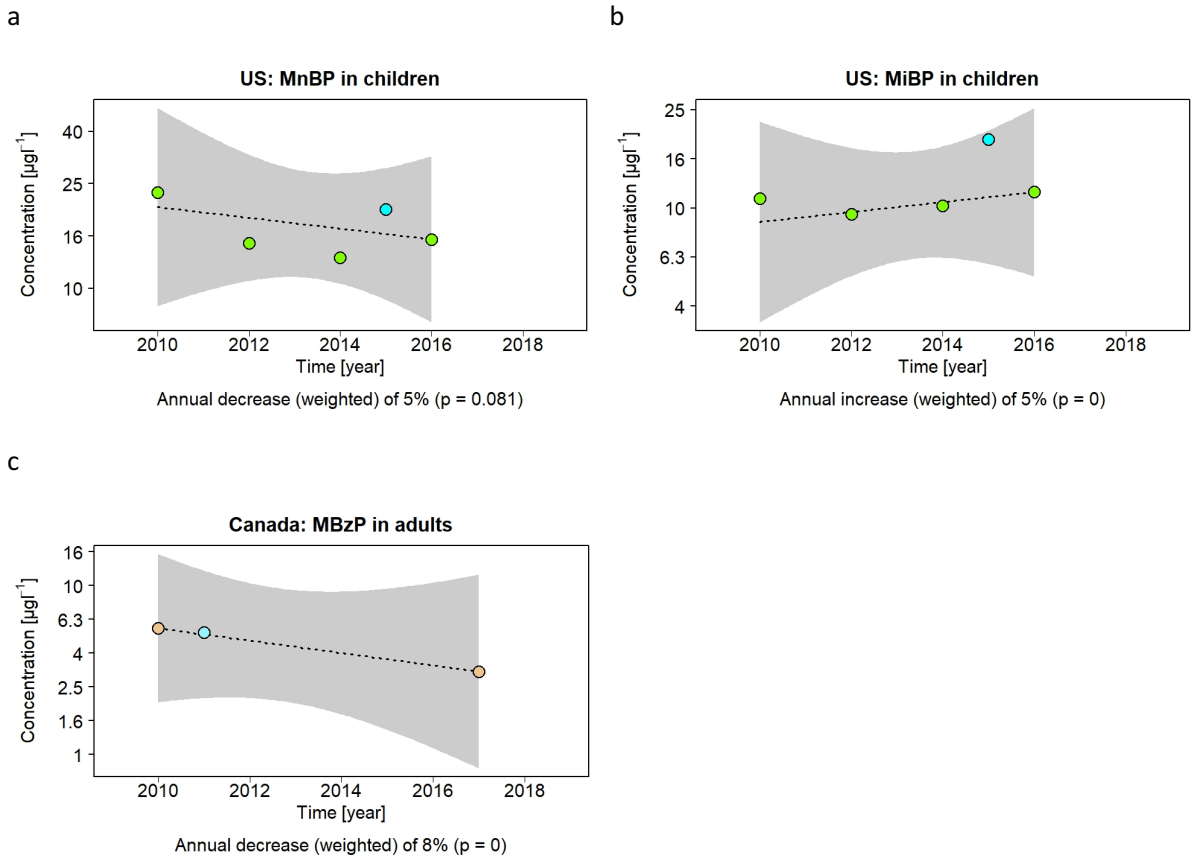


Figure S 6: time-trends in the urinary concentrations (µg/L) of: MnBP (DnBP metabolite) and MiBP (DiBP metabolite) in US children (panels a and b, respectively); MBzP (BBP metabolite) in Canadian adults (panel c)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Data from the same data source (Study ID number, see Data traceability in the "PhthaLit" database) are identified by symbols with the same colour in all panels and Figures. Grey area: 90% confidence interval. The p-value was < 0.001 for the trends shown in panels b and c

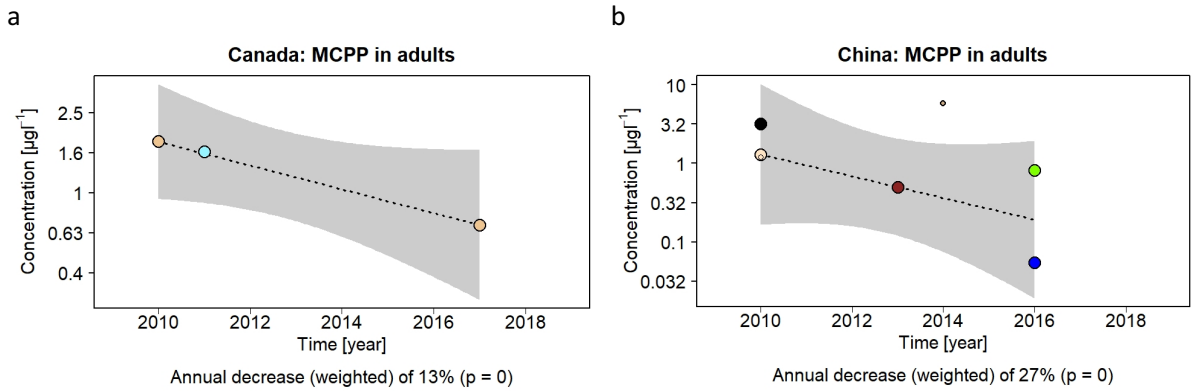


Figure S 7: time-trends in the urinary concentrations (µg/L) of MCPP in adults from Canada (panel a) and China (panel b)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Data from the same data source (Study ID number, see Data traceability in the "PhthaLit" database) are identified by symbols with the same colour in all panels and Figures. Grey area: 90% confidence interval. The p-value was < 0.001 for the trends shown in both panels

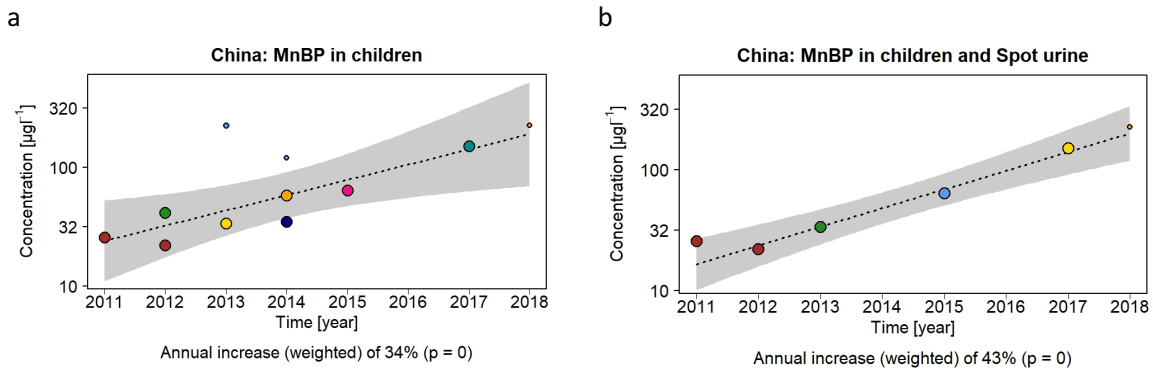
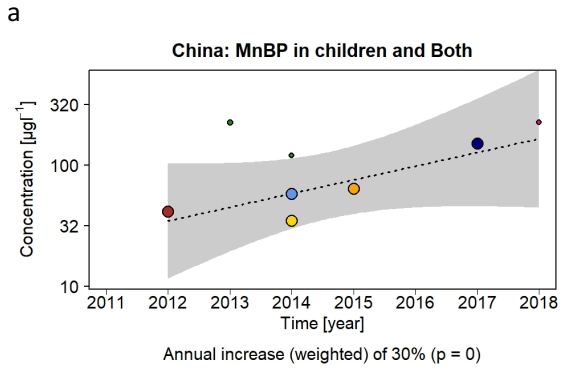


Figure S 8: time-trends for MnBP in Chinese children: a) including all data; b) per sample type (spot urine)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Within one panel, one colour identifies one Study ID number. However, in Figures S 8 to S 13, the colours are not comparable between panels and not comparable with the colours of other Figures in the manuscript. Grey area: 90% confidence interval. The p-value was < 0.001 for the trends shown in both panels



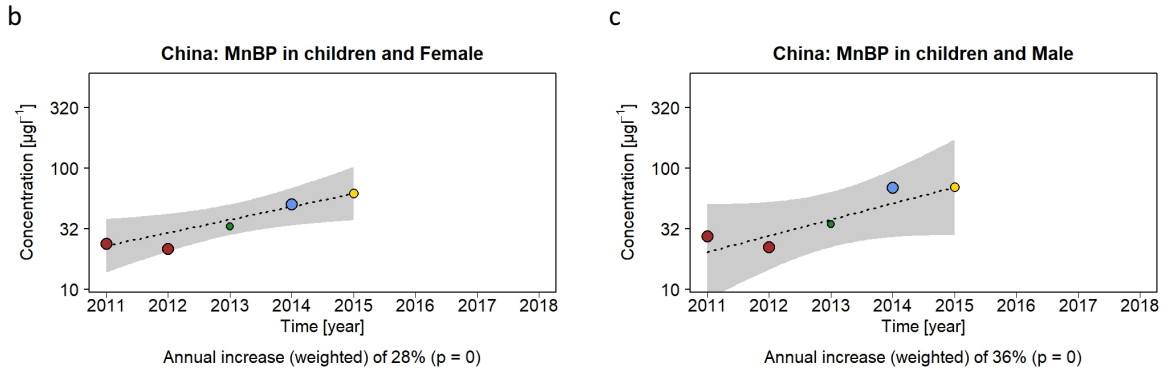


Figure S 9: significant time-trends for MnBP in Chinese children per gender (a, both genders; b, girls; c, boys)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Within one panel, one colour identifies one Study ID number. However, in Figures S 8 to S 13, the colours are not comparable between panels and not comparable with the colours of other Figures in the manuscript. Grey area: 90% confidence interval. The p-value was < 0.001 for the three trends

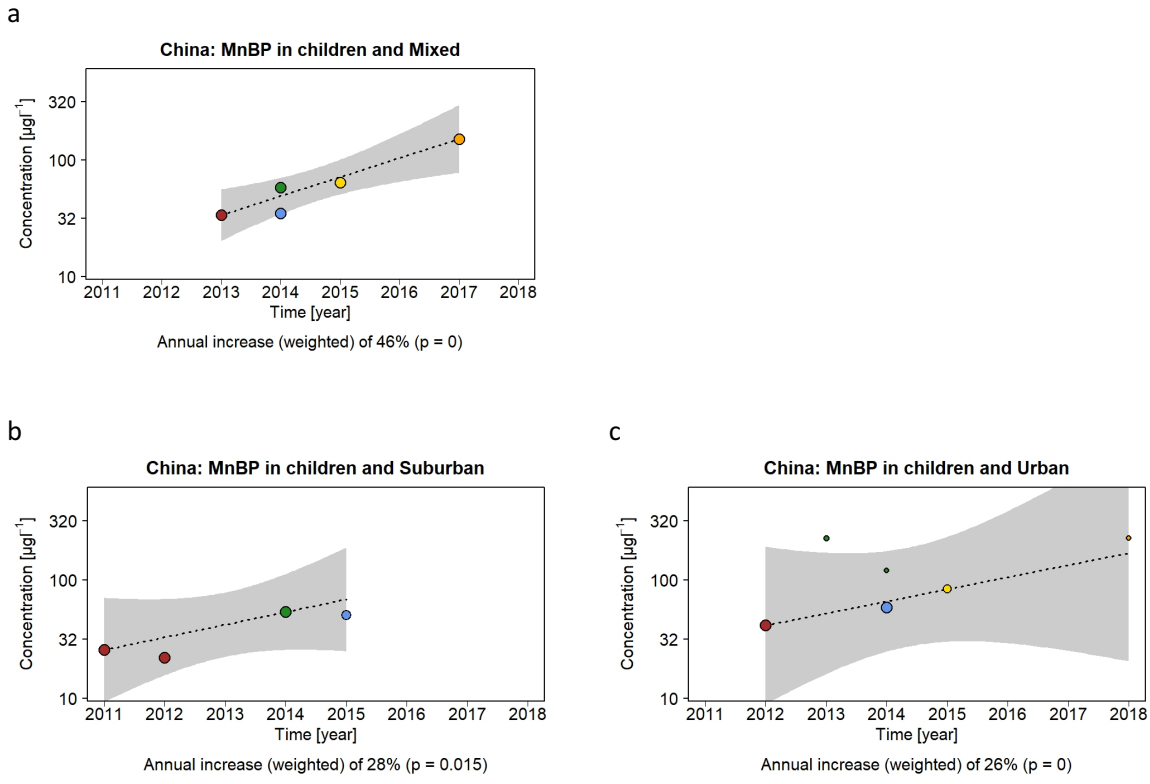


Figure S 10: significant time-trends for MnBP in Chinese children per area (a, mixed areas; b, suburban; c, urban)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Within one panel, one colour identifies one Study ID number. However, in Figures S 8 to S 13, the colours are not comparable between panels and not comparable with the colours of other Figures in the manuscript. Grey area: 90% confidence interval. The p-value was < 0.001 for the trends shown in panels a and c

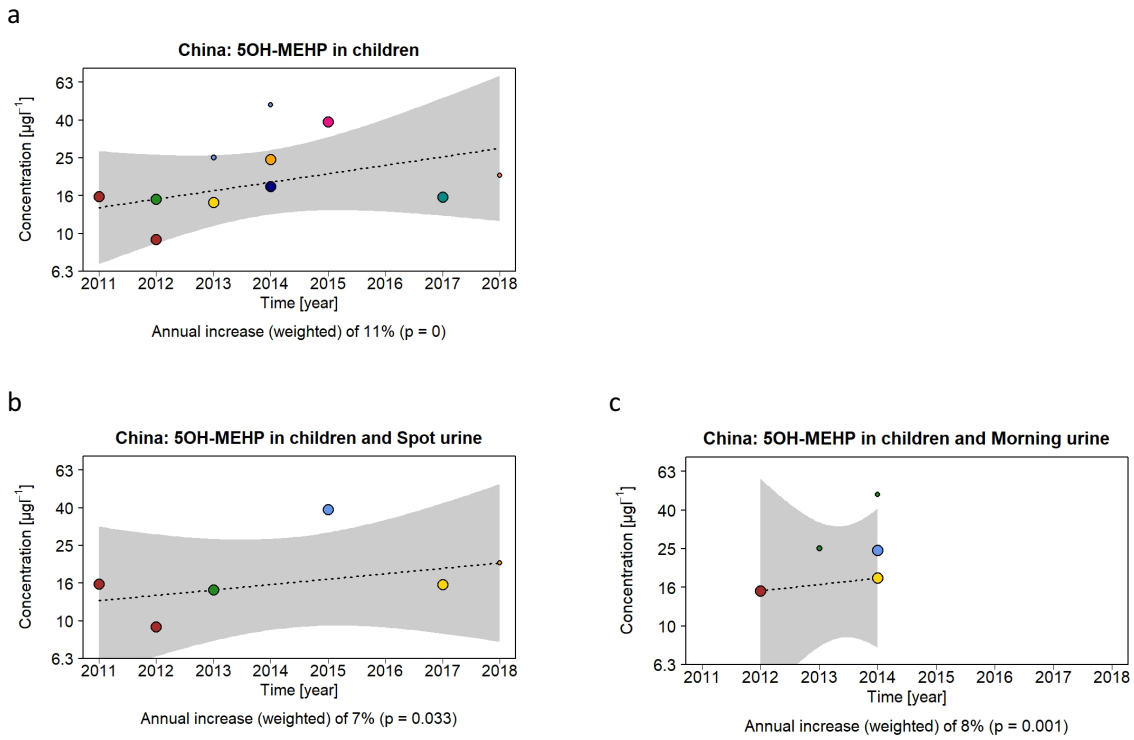
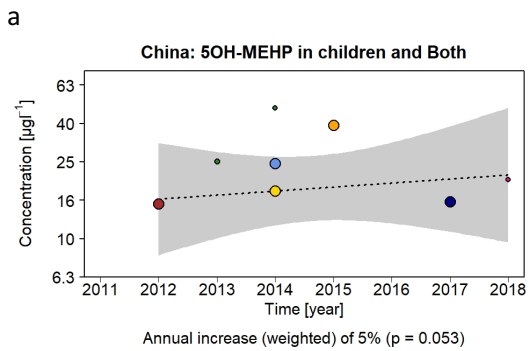


Figure S 11: time-trends for 5OH-MEHP in Chinese children: a) including all data; b) for data measured in spot urine; c) for data measured in morning urine

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Within one panel, one colour identifies one Study ID number. However, in Figures S 8 to S 13, the colours are not comparable between panels and not comparable with the colours of other Figures in the manuscript. Grey area: 90% confidence interval. The p-value was < 0.001 for the trend shown in panel a



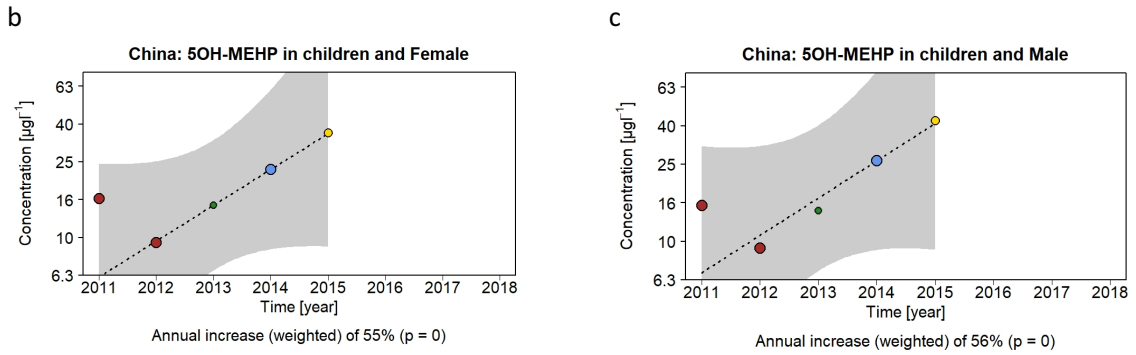


Figure S 12: significant time-trends for 5OH-MEHP in Chinese children per gender (a, both genders; b, girls; c, boys)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Within one panel, one colour identifies one Study ID number. However, in Figures S 8 to S 13, the colours are not comparable between panels and not comparable with the colours of other Figures in the manuscript. Grey area: 90% confidence interval. The p-value was < 0.001 for the trends shown in panels b and c

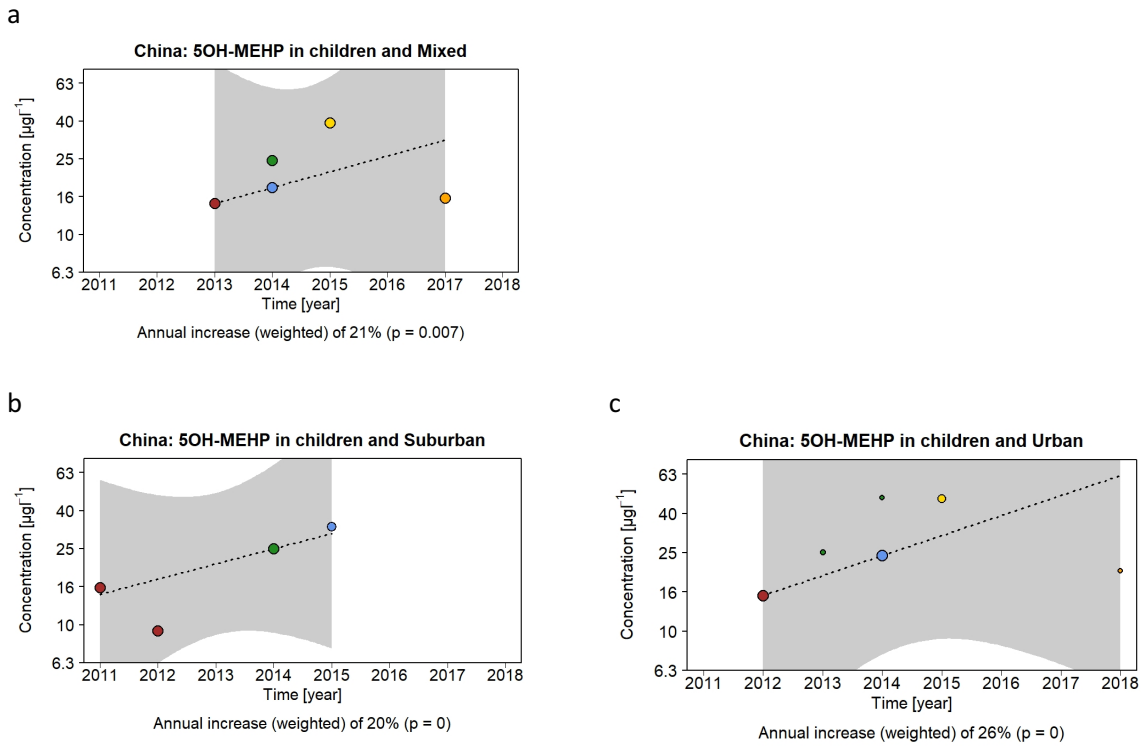
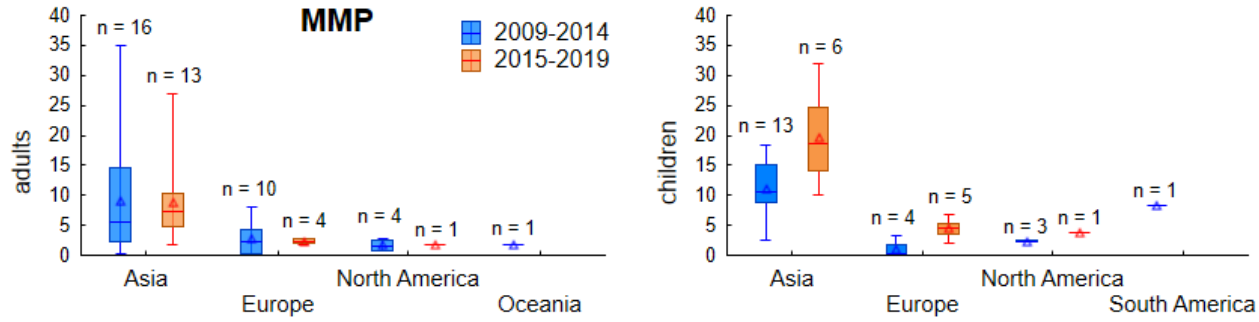


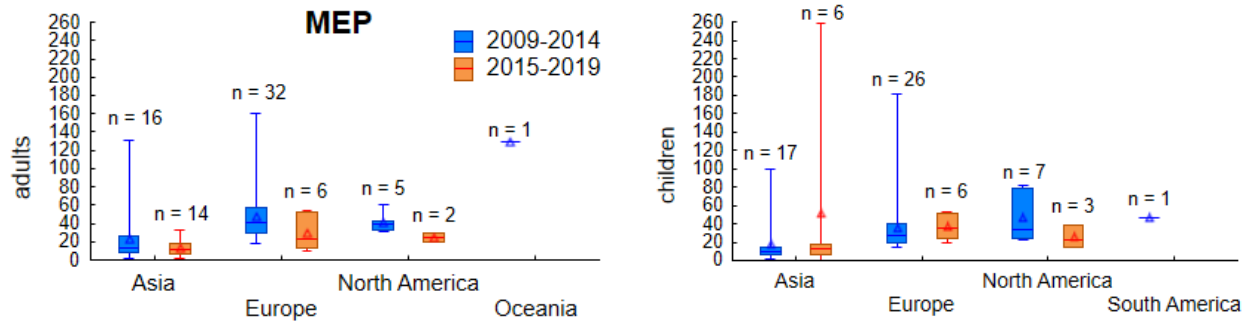
Figure S 13: significant time-trends for 5OH-MEHP in Chinese children per area (a, mixed areas; b, suburban; c, urban)

Each symbol is a central value (i.e. median or geometric mean). The size of the symbols is related to the study-specific sample size (N) and its weight in the time-trend calculation (see Statistical methods, time-trend analysis). Within one panel, one colour identifies one Study ID number. However, in Figures S 8 to S 13, the colours are not comparable between panels and not comparable with the colours of other Figures in the manuscript. Grey area: 90% confidence interval. The p-value was < 0.001 for the trends shown in panels b and c

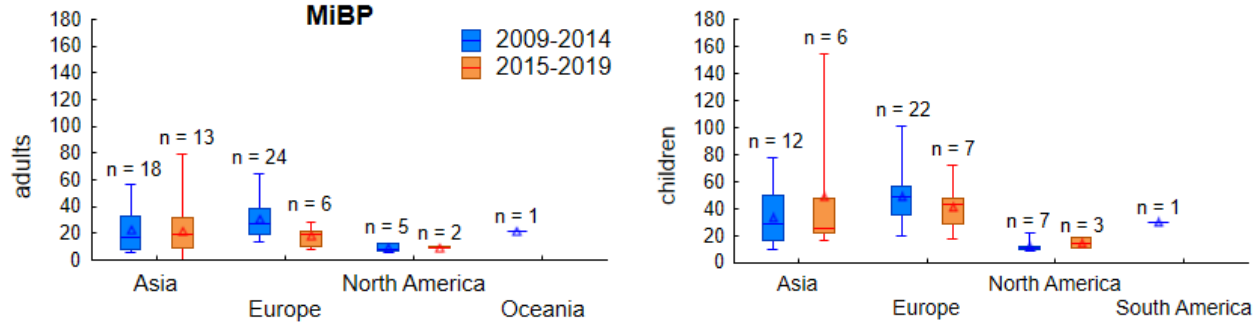
a)


MMP
2009-2014
2015-2019
adults
children
n = 16
n = 13
n = 10
n = 4
n = 4
n = 1
n = 1
n = 13
n = 6
n = 4
n = 5
n = 3
n = 1
n = 1
Asia
Europe
North America
Oceania
South America

b)


MEP
2009-2014
2015-2019
adults
children
n = 16
n = 14
n = 32
n = 6
n = 5
n = 2
n = 1
n = 17
n = 6
n = 26
n = 6
n = 7
n = 3
n = 1
Asia
Europe
North America
Oceania
South America

c)


MiBP
2009-2014
2015-2019
adults
children
n = 18
n = 13
n = 24
n = 6
n = 5
n = 2
n = 1
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n = 6
n = 22
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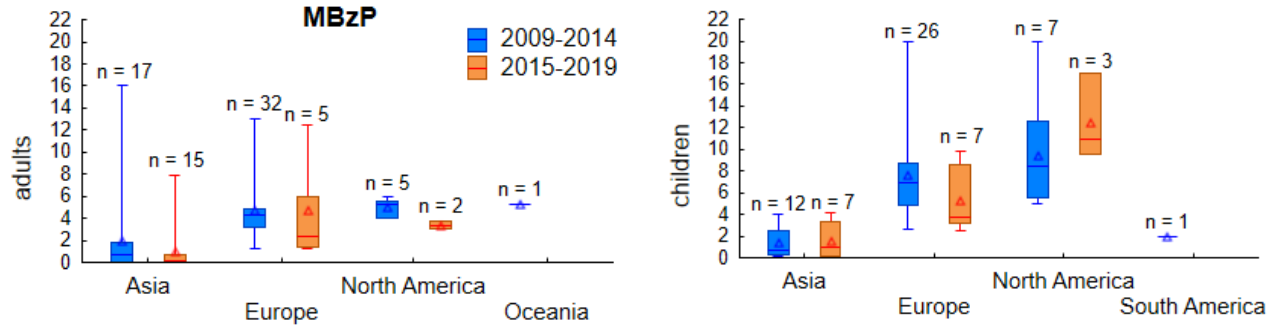
n = 7
n = 3
n = 1
Asia
Europe
North America
Oceania
South America

d)


MBzP
2009-2014
2015-2019
adults
children
n = 17
n = 15
n = 32
n = 5
n = 5
n = 2
n = 1
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n = 3
n = 1
Asia
Europe
North America
Oceania
South America

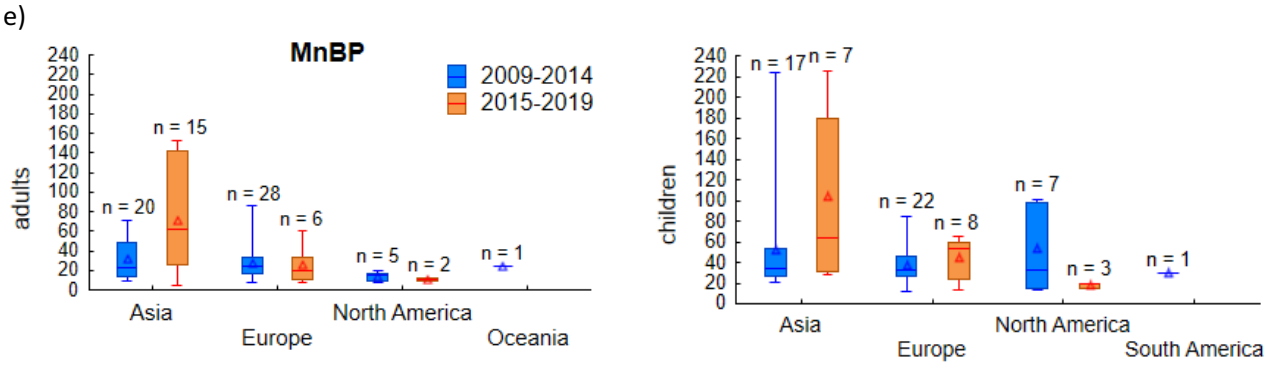

Figure S 14: boxplots of urinary concentrations (µg/L) of low-weight phthalates per continent and period (2009–2014 vs 2015–2019) in adults and children, for: MMP (a), MEP (b), MiBP (c), MBzP (d), and MnBP (e)

Triangular means average, line is median, box is 25-75th percentile range, whiskers are min.-max.

n is the number of central values per group. In the "PhthaLit" database, Egypt was classified as an Asian country.

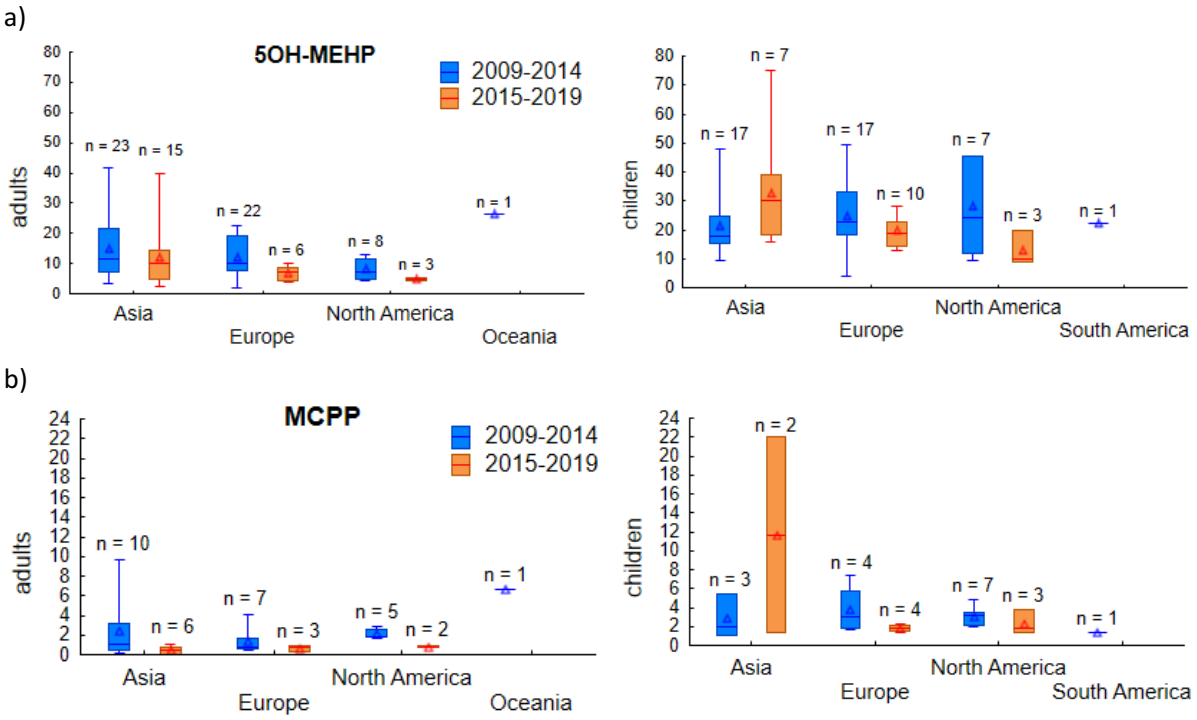

Figure S 15: boxplots of urinary concentrations (µg/L) per continent and period (2009–2014 vs 2015–2019) in adults and children, for: 5OH-MEHP (a), and MCPP (b)

Triangular means average, line is median, box is 25-75th percentile range, whiskers are min.-max. In the "PhthaLit" database, Egypt was classified as an Asian country.

S3. Additional information

S3.1. Urinary concentration units

For studies that reported only creatinine-corrected data, we aimed to back-calculate unadjusted values, by using Equation S 1:

Equation S 1
$$C_{\mathrm{Met(adj.Cr)}}\left(\frac{\mu g}{\text{g creatinine}}\right)\times C_{\mathrm{Creat}}\left(\frac{\text{g creatinine}}{\mathrm{L}}\right)=C_{\mathrm{Met(unadj)}}\left(\frac{\mu g}{\mathrm{L}}\right)$$

Where $C_{\mathrm{Met(adj.Cr)}}$ is the central value (median, geometric mean, GM) of creatinine-corrected concentration of metabolite in urine (µg/g creatinine), C_{Creat} is the central value (median, GM) of creatinine concentration in urine in the same samples (g creatinine/L), and $C_{\mathrm{Met(unadj)}}$ is the calculated unadjusted concentration of metabolite in urine (µg/L).

Among all studies in which phthalate concentrations were reported exclusively corrected by creatinine, one study in Taiwanese children by Su et al. (17) reported the geometric mean of creatinine concentrations measured in the same samples. Therefore, we back-calculated unadjusted phthalate concentrations for this study by using Equation S 1. Conversely, in other studies we were not able to find the median or GM value of measured creatinine concentrations. For the last studies, no unadjusted phthalate concentrations could be calculated and therefore, the reported data (in µg/g creatinine) were excluded from the data analysis.

S3.2. Correction of censored data

To deal with data below the limit of detection (LOD, left censoring) or below the limit of quantification (LOQ, interval censoring), different methods exist (18). For example, Helsel, 1990 (19) recommended maximum likelihood estimation (MLE) methods to estimate percentiles, and robust methods to estimate mean and standard deviation values. The selection of methods also depends on the percentage of censored data (18, 20).

In the publications from which censored data were compiled, substitution was the most frequent approach used to deal with censored data. Between substitution methods, replacing the data <LOD by either LOD/2 or by LOD/√2 made little difference in the estimates of geometric means by CDC (2). In our database, the central values reported to be <LOD or <LOQ were replaced by LOD/2 and LOQ/2, respectively. Few exceptions were made, for publications which reported non-detected central values (i.e. <LOD) and showed LOQ values rather than LOD values (21-25). In these specific cases, we replaced the central values <LOD by LOQ/2. Moreover in Lee I. et al. (23), the LOQ values for individual metabolites were not shown but they were reported to oscillate between 0.01 and 0.05 ng/mL. Therefore, to correct censored data in that publication, we considered an average LOQ value of 0.03 ng/mL.

S3.3. Impact of the gender, area, and sample type on the time-trends

In the literature, some HBM studies have found an impact of variables such as the gender, the sample type, or the area on phthalate concentrations in urine. Concerning the gender, we found no consensus in the literature about the possible impact of this variable on unadjusted phthalate concentrations in urine (µg/L). For example, some HBM studies have reported gender differences (34, 75), while others

have generally found no significant gender differences on the unadjusted phthalate concentrations (12, 13). Concerning the sample type, a relatively high within-day variability in phthalate concentrations in urine has been reported, with high concentrations in morning urine as compared to spot urine collected in the afternoon (76-78). Finally, some HBM studies have found differences between urban, suburban and/or rural areas in Asian countries (37, 79, 80). Between these variables, information on the gender and the sample type (spot urine, morning urine, 24-h urine) is generally shown in the HBM studies. Conversely, the area (urban, suburban, rural, mixed) is generally not specified. Therefore, for the analysis of the impact of the area on the time-trends, we focused specifically on China, where a high number of data sources was included in the time-trend analyses and a higher variability was expected. In summary, we analysed the impact of the gender and sample type on the time-trends in all countries, and the impact of the area on the time-trends in China. Specifically, all time-trend analyses were conducted separately per gender, area, and sample type, and compared to the original trends using Fisher z-scoring (81). None of these variables had a significant impact in any trend. The p-value of the trend difference test (81) was in all cases higher than 0.10.

For example, the global time-trends for MnBP in Chinese children (Figures 4b and S 8a) can be compared to the significant time-trends for MnBP in Chinese children calculated separately per sample type (Figure S 8b), gender (Figure S 9), and area (Figure S 10). Similarly, the global trend for 5OH-MEHP in Chinese children (Figure S 11 a) can be compared to the trends calculated separately per sample type (Figure S 11 b, c), gender (Figure S 12), and area (Figure S 13).

S3.4. Geographic comparisons

Geographic comparisons in the unadjusted urinary concentrations per substance, continent, and age group, were conducted. For these comparisons, we classified the data into two periods, specifically 2009–2014 and 2015–2019. Per parent substance, we selected either one monoester (for low-weight phthalates) or one secondary metabolite (for other phthalates and plasticizers). The selection of metabolites was also based on the number of data and the level of censoring (<=33%) per period and substance.

Different from the approach used for time-trend analysis, for geographic comparisons we included as variables: a) the continent (including Europe) instead of the country, and b) two sampling periods instead of study-specific sampling years. Also different from the time-trend analysis, for geographic comparisons we did not calculate the median value per metabolite, continent, age group, Study ID, and year. Therefore, to avoid duplicates in geographic comparisons, we excluded data reported for different subgroups (gender, area) of the same population (same Study ID and year).

Within one continent, the number of data differed between countries. For example, a high amount of data was available in China and Germany both for adults and children (Table S 3 and Table S 4) and, by consequence, data from these countries had a high weight within their continents. Interestingly, for some countries, a high amount of data existed principally either in adults (Denmark and Korea) or in children (e.g. Taiwan). Thus, if geographic differences were consistent between age groups, we considered these results to be important. Given the higher amount of data in Asia (As), Europe (Eu), and North America (NA), than in other continents, we compared the averages of central values in these three continents.

In brief, the averages of the compiled central values differed consistently between continents for both age groups and periods for: MMP (As > Eu and NA), MEP (Eu and NA > As), MiBP (Eu >= As > NA), and MBzP (NA > Eu > As) (Figure S 14, a-d). In Asia, for MnBP in adults and children, MMP and 5OH-MEHP

in children, the average concentrations increased from the first to the second period and were higher in this continent than in others for the second period (Figures S 14 a, e; S 15a). For other metabolites, either no consistent differences between continents for both age groups and periods were found (e.g. MCPP; Figure S 15b), or the number of data did not allow geographic comparisons (cx-MINP, OH-MINCH, 5OH-MEHTP; not shown).

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