

Supplementary Materials

Exposure and risk assessment of organophosphate flame retardants in Egyptian, Bangladeshi, Thai, Indonesian and South Korean children

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Supplementary TEXT

Supplementary Text 1. Chemicals and materials

Di-n-butylphosphate (DNBP), diphenyl phosphate (DPHP) and the internal standards DPHP-d10 and TPHP-d15 were obtained from Sigma-Aldrich (Bornem, Belgium). Hydroxyphenyl diphenyl phosphate (HO-TPHP), hydroxyphenyl phenyl phosphate (HO-DPHP), bis(2-butoxyethyl) 3'-hydroxy-2-butoxyethyl phosphate (3-HO-TBOEP), bis(2-butoxyethyl) phosphate (BBOEP), 2-hydroxyethyl bis(2-butoxyethyl) phosphate (BBOEHEP), 1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP), bis (1-chloro-2-propyl) phosphate (BCIPP), bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), 2-ethylhexyl phenyl phosphate (EHPHP), 2-ethyl-5-hydroxyhexyl diphenyl phosphate (5-HO-EHDPHP) and the internal standards TCEP-D12, BBOEHEP-D4, BBOEP-D4, BDCIPP-D10, and TBOEP-D6 were custom synthesized by Dr. Vladimir Belov (Max Planck Institute, Göttingen, Germany). Tris (chloroethyl) phosphate (TCEP) was purchased from Chiron AS (Trondheim, Norway). Methanol (LC-MS grade) was purchased from Biosolve (Valkenswaard, Netherlands). Potassium phosphate, potassium hydroxide, formic acid and ammonium acetate and β -glucuronidase (lyophilized powder from *Escherichia coli*, > 10,000,000 unit/g) were all of analytical grade and obtained from Merck (Darmstadt, Germany). Ultrapure water was generated from a PURELAB Flex system (ρ =18.2 M Ω /cm, Elga Veolia, Tienen, Belgium).

Supplementary Text 2. Measurement of organophosphate flame retardant metabolites in urine

Organophosphate flame retardant (PFR) metabolites were extracted and measured using a previously validated method [1] with instrumental parameters adapted for the Agilent 6495 Triple Quadrupole Mass Spectrometer (Table S2 and S3). Briefly, 1 mL of urine was spiked with internal standard mixture (5 ng) and adjusted to pH 6 using phosphate buffer. To achieve deconjugation of glucuronide metabolites, β -glucuronidase enzyme (lyophilized powder from *Escherichia coli*, >10,000,000 unit/g, 50 μ L of 2 mg/mL) was added to each sample. Samples were incubated for 2 hours at 37 °C and extracted using Bond Elut C18 cartridges (3 mL, 200 mg, Agilent Santa Clara, USA) conditioned with 3 mL methanol and 2 mL MilliQ. Elution of target analytes was achieved with 3 mL methanol. After evaporation until near dryness, samples were reconstituted in 100 μ L methanol:MilliQ (1:1, v/v) and filtered using centrifugal filters (0.2 μ m, nylon, VWR, Leuven, Belgium). Extracts were injected on an Agilent 1290 Infinity liquid chromatography system coupled to a triple quadrupole mass spectrometer (ESI-6495, Agilent). Separation of analytes was achieved using a biphenyl column (2.1 mm x 100 mm, 2.6 μ m; Phenomenex Kinetex, Torrance, USA). MilliQ with 2% methanol and 5 mM ammonium acetate was used as mobile phase A, while mobile phase B consisted of methanol with 2% MilliQ and 5 mM ammonium acetate. Samples were analyzed using dynamic multiple reaction monitoring switching between positive and negative ionization mode.

Supplementary Text 3. Measurement of specific gravity and creatinine

Both specific gravity and creatinine content in the urine samples were measured at the national university of Seoul, South Korea. Specific gravity in the urine samples was measured with a digital refractometer (PAL-10S, ATAGO, Japan). To correct for specific gravity (SG) the following formula was used[2]:

$$conc_{SG} = conc * \frac{SG_{ref} - 1}{SG_{sample} - 1}$$

In this formula, $conc_{SG}$ is the specific gravity corrected concentration in ng/mL, $conc$ is the unadjusted concentration in ng/mL, SG_{ref} is the median specific gravity (1.0185 in this study) of all the samples, and SG_{sample} is the specific gravity of the sample itself. Urinary creatinine was measured using the Cobas 8000 (c702) (Roche, Switzerland) with the Kinetic Jaffe without compensation method.

Supplementary Tables

Supplementary Table 1. Parent compounds and their measured metabolites in the current study. The accuracy of the QCs and LOQs for metabolites are displayed as well.

Parent compound	Abbreviation	Metabolite	Abbreviation	Accuracy of QC (%) (n=24)	LOQ (ng/mL)
Tris (1-chloro-2-propyl) phosphate	TCIPP	Bis(1-chloro-2-propyl) phosphate	BCIPP	103	1.00
		1-hydroxy-2-propyl bis (1-chloro-2-propyl) phosphate	BCIPHIPP	103	0.04
		4-hydroxyphenyl phosphate	4-HO-DPHP	61	0.50
Triphenyl phosphate	TPHP	Diphenyl phosphate	DPHP	118, 110*	0.10
		Hydroxyphenyl diphenyl phosphate	HO-TPHP	69	0.01
		Bis (1,3-dichloro-2-propyl) phosphate	BDCIPP	115, 91*	0.05
Tris (1,3-dichloro-2-propyl) phosphate	TDCIPP	2-ethyl-5-hydroxyhexyl diphenyl phosphate	5-HO-EHDPHP	132	0.01
		2-ethylhexyl phenyl phosphate	EHPHP	172	0.05
		Bis (2-butoxyethyl) phosphate	BBOEP	102	0.05
2-ethylhexyldiphenyl phosphate	EHDPHP	Bis (2-butoxyethyl) 3'-hydroxy-2-butoxyethyl phosphate	TBOEP-OH	130	0.01
		Di-n-butyl phosphate	DNBP	138	0.15
		Bis (2-ethylhexyl) phosphate	BEHP	116	0.10
Tris (2-butoxyethyl) phosphate	TBOEP	Tris (chloroethyl) phosphate	TCEP [#]	104	0.04

*QC from OSEQAS (n=36 injections) #TCEP is a parent compound, but due to low hepatic clearance the parent compound is monitored rather than the metabolite

Supplementary Table 2. MS settings for analysis of PFR metabolites on the Agilent 6495 QQQ.

Parameter	Value (+ESI)	Value (-ESI)
Dry gas temperature (° C)	250	250
Dry gas flow (L/min)	14	14
Nebulizer (psi)	40	40
Sheath gas temperature (° C)	325	325
Sheath gas flow (L/min)	11	11
Capillary (V)	3000	2500
Nozzle (V)	0	0
High pressure RF	130	70
Low pressure RF	60	40

Supplementary Table 3. Instrumental parameters for the measured PFR metabolites on the Agilent 6495 QQQ.

Compound	IS	Precursor (m/z)	Product ion (m/z)	CE (V)	FV (V)	CAV (V)	Polarity
4-HO-DPHP	DHP-d10	265	108	50	166	2	Negative
		265	93	40		2	
5-HO-EHDPHP	TPHP-d15	379	251	10	166	6	Positive
		379	153	35		6	
BBOEP	BBOEP-d4	297	197	20	166	4	Negative
		297	79	30		2	
BCIPP	BDCIPP-d10	251	35	10	166	2	Negative
		249	35	5		2	
BCIPHIPP	TCEP-d12	309	175	10	166	6	Positive
		309	99	25		2	
BDCIPP	BDCIPP-d10	319	37	15	166	2	Negative
		317	35	10		2	
BEHP	BEHP-d34	321.3	209.1	20	166	4	Negative
		321.3	79	35		2	
DNBP	DNBP-d18	209	152.9	10	166	6	Negative
		209	78.9	30		2	
DHP	DHP-d10	249	155	20	166	6	Negative
		249	93	35		2	
EHPHP	DHP-d10	285	93	45	166	2	Negative
		285	79	25		2	
HO-TPHP	DHP-d10	341	249	20	166	4	Negative
		341	93	55		2	
TBOEP-OH	TBOEP-d6	415	99	40	166	2	Positive
		415	45	30		6	
TCEP	TCEP-d12	285	99	25	166	2	Positive
		285	63	30		6	

IS: Internal Standard CE: collision energy FV: fragmentor voltage CAV: collision cell accelerator voltage

Supplementary Table 4 is provided as Excel.

Supplementary Table 5. Included parent compounds in EDI and RCR calculations. Metabolites on which calculations were based are displayed. The F_{UE} values used to calculate the EDI and the DNEL used to calculate the RCR are displayed for each compound.

Parent Compound	Metabolite	F_{UE}	DNEL (ng/kg bw/day)
TPHP	DHP	0.19 ^a	525 000 ^c
TDCIPP	BDCIPP	0.46 ^a	17 000 ^c
TCIPP	BCIPHIPP	0.28 ^a	10 000 ^d
EHDPHP	EHPHP	0.2 ^b	36 000 ^c
	5-HO-EHDPHP		

^aAccording to Van den Eede et al., 2013^[3]

^bFor EHPHP and 5-HO-EHDPHP kinetic data are scarce, therefore a value of 0.2 was chosen to reflect a low excretion and therefore high exposure scenario

^cAs established by ECHA^[4]

^dAs established by the US EPA^[5]

Supplementary Table 6. Detection frequencies and concentrations (ng/mL, uncorrected) in urine from children from 5 different countries (n=502). The geometric mean (GM) is displayed for compounds with DF > 50%.

Parent compound	Metabolite	DF (%)	GM	median (IQR)	95th
TCIPP	BCIPP	2		<LOQ (<LOQ-<LOQ)	<LOQ
	BCIPHIPP	90	0.27	0.26 (0.10-0.70)	2.66
	4-HO-DPHP	47		<LOQ (<LOQ-1.16)	5.94
TPHP	DPHP	90	0.47	0.49 (0.21-0.93)	2.6
	HO-TPHP	29		<LOQ (<LOQ-0.01)	0.04
TDCIPP	BDCIPP	90	0.15	0.14 (0.09-0.25)	0.62
EHDPHP	EHPHP	55	0.04	0.04 (<LOQ-0.09)	0.22
	5-HO-EHDPHP	75	0.02	0.02 (0.01-0.05)	0.14
TBOEP	BBOEP	4		<LOQ (<LOQ-<LOQ)	<LOQ
	TBOEP-OH	4		<LOQ (<LOQ-<LOQ)	<LOQ
TNBP	DNBP	21		<LOQ (<LOQ-<LOQ)	5.94
TEHP	BEHP	1		<LOQ (<LOQ-<LOQ)	<LOQ
TCEP	TCEP	17		<LOQ (<LOQ-<LOQ)	1.68

Supplementary Table 7. Detection frequencies and concentrations of PFR metabolites (ng/mL, SG corrected) in children from 5 countries (n=502). The geometric mean is displayed for compounds with DF > 50%.

Parent compound	Metabolite	DF (%)	GM	median (IQR)	95th
TCIPP	BCIPP	2		<LOQ (<LOQ-<LOQ)	<LOQ
	BCIPHIPP	90	0.29	0.26 (0.11-0.64)	2.28
	4-HO-DPHP	47		<LOQ (<LOQ-1.16)	5.67
TPHP	DPHP	90	0.50	0.49 (0.27-0.81)	2.11
	HO-TPHP	29		<LOQ (<LOQ-0.01)	0.04
TDCIPP	BDCIPP	90	0.16	0.15 (0.09-0.25)	0.56
EHDPHP	EHPHP	55	0.05	0.05 (<LOQ-0.07)	0.17
	5-HO-EHDPHP	75	0.03	0.03 (0.01-0.04)	0.12
TBOEP	BBOEP	4		<LOQ (<LOQ-<LOQ)	<LOQ
	TBOEP-OH	4		<LOQ (<LOQ-<LOQ)	<LOQ
TNBP	DNBP	21		<LOQ (<LOQ-<LOQ)	0.35
TEHP	BEHP	1		<LOQ (<LOQ-<LOQ)	<LOQ
TCEP	TCEP	17		<LOQ (<LOQ-<LOQ)	0.12

Supplementary Table 8. Detection frequencies and concentrations (µg/g creatinine) in urine from children from 5 different countries (n=502). The geometric mean (GM) is displayed for compounds with DF > 50%.

Parent compound	Metabolite	DF (%)	GM	median (IQR)	95th
TCIPP	BCIPP	2		<LOQ (<LOQ-<LOQ)	<LOQ
	BCIPHIPP	90	0.29	0.27 (0.12-0.61)	1.93
	4-HO-DPHP	47		<LOQ (<LOQ-1.22)	5.8
TPHP	DPHP	90	0.5	0.48 (0.27-0.83)	2.41
	HO-TPHP	29		<LOQ (<LOQ-0.01)	0.04
TDCIPP	BDCIPP	90	0.16	0.16 (0.09-0.26)	0.61
EHDPHP	EHPHP	55	0.05	0.05 (<LOQ-0.07)	0.18
	5-HO-EHDPHP	75	0.03	0.02 (0.01-0.04)	0.11
TBOEP	BBOEP	4		<LOQ (<LOQ-<LOQ)	<LOQ
	TBOEP-OH	4		<LOQ (<LOQ-<LOQ)	<LOQ
TNBP	DNBP	21		<LOQ (<LOQ-<LOQ)	0.39
TEHP	BEHP	1		<LOQ (<LOQ-<LOQ)	<LOQ
TCEP	TCEP	17		<LOQ (<LOQ-<LOQ)	0.14

Supplementary Table 9. Detection frequencies and concentrations of PFR metabolites (ng/mL, uncorrected for SG) in urine of children from 5 different countries displayed separate for each country. The geometric mean (GM) is displayed only for compounds with a DF > 50%.

Parent compound	Metabolite	Egypt				Bangladesh				Thailand				Indonesia				South Korea			
		DF (%)	G M	median (IQR)	95th	DF (%)	G M	median (IQR)	95th	DF (%)	G M	median (IQR)	95th	DF (%)	G M	median (IQR)	95th	DF (%)	G M	median (IQR)	95th
TCIPP	BCIPP	2		<LOQ	<LOQ	1		<LOQ	<LOQ	2		<LOQ	<LOQ	1		<LOQ	<LOQ	7		<LOQ	1.1
	BCIPHIPP	82	0.1 1	0.11 (0.05-0.23)	0.48	79	0.1 0	0.11 (0.05-0.17)	0.39	92	0.2 8	0.25 (0.10-0.69)	2.61	96	0.4 6	0.48 (0.23-0.88)	2.87	100	1.1 1	1.03 (0.58-1.64)	6.77
TPHP	4-HO-DPHP	74	1.0 5	1.05 (<LOQ-2.29)	11.64	41		<LOQ (<LOQ-0.67)	1.9	42		<LOQ (<LOQ-0.98)	2	19		<LOQ	1.14	64	1.0 1	1.15 (<LOQ-2.76)	13.48
	DPHP	99	0.5 8	0.62 (0.33-0.94)	1.55	71	0.2 2	0.17 (0.09-0.44)	1.02	95	0.5 1	0.52 (0.27-0.87)	1.88	87	0.3 4	0.33 (0.17-0.62)	1.78	98	1.1 0	1.01 (0.55-2.08)	6.27
TDCIPP	HO-TPHP	65	0.0 1	0.01 (<LOQ-0.02)	0.06	17		<LOQ (<LOQ-<LOQ)	0.03	26		<LOQ (<LOQ-0.01)	0.03	15		<LOQ	0.03	21		<LOQ	0.03
	BDCIPP	86	0.1 2	0.11 (0.08-0.17)	0.38	91	0.1 4	0.11 (0.08-0.17)	0.54	94	0.1 7	0.16 (0.11-0.24)	0.88	80	0.1 0	0.10 (0.06-0.15)	0.3	99	0.3 0	0.31 (0.23-0.40)	0.7
EHDPHP	EHPHP	75	0.0 5	0.05 (<LOQ-0.09)	0.15	22		<LOQ	0.11	55	0.0 5	0.05 (<LOQ-0.11)	0.21	52	0.0 4	0.04 (<LOQ-0.09)	0.19	76	0.0 7	0.07 (0.04-0.11)	0.44
	5-HO-EHDPHP	90	0.0 3	0.03 (0.02-0.06)	0.16	29		<LOQ (<LOQ-0.01)	0.02	91	0.0 4	0.04 (0.02-0.07)	0.15	74	0.0 2	0.02 (<LOQ-0.03)	0.09	94	0.0 4	0.03 (0.02-0.07)	0.22
TBOEP	BBOEP	0		<LOQ	<LOQ	14		<LOQ	0.09	2		<LOQ	<LOQ	2		<LOQ	<LOQ	2		<LOQ	<LOQ
	TBOEP-OH	0		<LOQ	<LOQ	0		<LOQ	<LOQ	15		<LOQ	0.8	0		<LOQ	<LOQ	2		<LOQ	<LOQ
TNBP	DNBP	11		<LOQ	0.24	38		<LOQ (<LOQ-0.18)	0.32	19		<LOQ	0.25	14		<LOQ	0.51	24		<LOQ	0.51
TEHP	BEHP	0		<LOQ	<LOQ	1		<LOQ	<LOQ	1		<LOQ	<LOQ	2		<LOQ	<LOQ	3		<LOQ	<LOQ
TCEP	TCEP	5		<LOQ	0.02	2		<LOQ	<LOQ	17		<LOQ	0.13	9		<LOQ	0.07	54	0.0 3	0.06 (<LOQ-0.10)	0.19

Supplementary Table 10. Detection frequencies and concentrations of PFR metabolites (µg/g creatinine) in urine of children from 5 different countries displayed separate for each country. The geometric mean (GM) is displayed only for compounds with a DF > 50%.

Parent compound	Metabolite	Egypt				Bangladesh				Thailand				Indonesia				South Korea			
		DF (%)	G M	median (IQR)	95th	DF (%)	G M	median (IQR)	95th	DF (%)	G M	median (IQR)	95th	DF (%)	G M	median (IQR)	95th	DF (%)	G M	median (IQR)	95th
TCIPP	BCIPP	2		<LOQ	<LOQ	1		<LOQ	<LOQ	2		<LOQ	<LOQ	1		<LOQ	<LOQ	7		<LOQ	0.71
	BCIPHIPP	82	0.13	0.11 (0.07-0.25)	0.49	79	0.15	0.15 (0.09-0.25)	0.49	92	0.28	0.23 (0.10-0.57)	2.3	96	0.41	0.37 (0.22-0.62)	1.91	100	0.99	0.83 (0.62-1.26)	5.57
	4-HO-DPHP	74	1.17	1.23 (<LOQ-2.76)	12.3	41		<LOQ (<LOQ-0.97)	1.88	42		<LOQ (<LOQ-0.77)	2.24	19		<LOQ	1.19	64	0.90	1.05 (<LOQ-2.14)	17.54
TPHP	DPHP	99	0.64	0.62 (0.40-0.91)	1.66	71	0.33	0.30 (<LOQ-0.53)	1.2	95	0.53	0.50 (0.32-0.75)	1.76	87	0.31	0.28 (0.18-0.49)	1.16	98	0.99	0.91 (0.54-1.83)	5.78
	HO-TPHP	65	0.01	0.01 (<LOQ-0.02)	0.05	17		<LOQ	0.01	26		<LOQ (<LOQ-0.01)	0.02	15		<LOQ	0.02	21		<LOQ (<LOQ-<LOQ)	0.02
TDCIPP	BDCIPP	86	0.14	0.13 (0.08-0.19)	0.49	91	0.20	0.18 (0.11-0.28)	0.86	94	0.18	0.17 (0.11-0.25)	0.83	80	0.09	0.09 (0.06-0.14)	0.29	99	0.27	0.28 (0.20-0.40)	0.62
EHDPHP	EHPHP	75	0.05	0.05 (<LOQ-0.08)	0.13	22		<LOQ	0.19	55	0.05	0.05 (<LOQ-0.08)	0.14	52	0.04	0.04 (<LOQ-0.06)	0.12	76	0.06	0.06 (0.04-0.10)	0.26
	5-HO-EHDPHP	90	0.04	0.04 (0.02-0.06)	0.15	29		<LOQ (<LOQ-0.02)	0.03	91	0.04	0.04 (0.02-0.06)	0.12	74	0.02	0.02 (<LOQ-0.03)	0.06	94	0.03	0.03 (0.02-0.05)	0.15
TBOEP	BBOEP	0		<LOQ	<LOQ	14		<LOQ	0.13	2		<LOQ	<LOQ	2		<LOQ	<LOQ	2		<LOQ	<LOQ
	TBOEP-OH	0		<LOQ	<LOQ	0		<LOQ	<LOQ	15		<LOQ	0.67	0		<LOQ	<LOQ	2		<LOQ	<LOQ
TNBP	DNBP	11		<LOQ	0.21	38		<LOQ (<LOQ-0.21)	0.56	19		<LOQ	0.22	14		<LOQ	0.34	24		<LOQ	0.46
TEHP	BEHP	0		<LOQ	<LOQ	1		<LOQ	<LOQ	1		<LOQ	<LOQ	2		<LOQ	<LOQ	3		<LOQ	<LOQ
TCEP	TCEP	5		<LOQ	0.13	2		<LOQ	<LOQ	17		<LOQ	0.15	9		<LOQ	0.08	54	0.03	0.05 (<LOQ-0.09)	0.2

Supplementary Table 11. Differences in DPHP concentrations between the different countries. A Kruskal-Wallis test with adjusted p-values for pairwise comparisons was performed with $p \leq 0.05$ for the adjusted p-value considered significant.

DPHP	Bangladesh	Egypt	Indonesia	South Korea	Thailand
Bangladesh		<u>< 0.001*</u>	1.000	<u>< 0.001*</u>	<u>< 0.001*</u>
Egypt			<u>< 0.001*</u>	0.083	1.000
Indonesia				<u>< 0.001*</u>	<u>0.008*</u>
South Korea					<u>≤ 0.001*</u>
Thailand					

Significant values are underlined and indicated with an asterisk.

Supplementary Table 12. Differences in BDCIPP concentrations between the different countries. A Kruskal-Wallis test with adjusted p-values for pairwise comparisons was performed with $p \leq 0.05$ for the adjusted p-value considered significant.

BDCIPP	Bangladesh	Egypt	Indonesia	South Korea	Thailand
Bangladesh		<u>0.027*</u>	<u>< 0.001*</u>	<u>< 0.001*</u>	1.000
Egypt			1.000	<u>< 0.001*</u>	<u>0.014*</u>
Indonesia				<u>< 0.001*</u>	<u>< 0.001*</u>
South Korea					<u>< 0.001*</u>
Thailand					

Significant values are underlined and indicated with an asterisk.

Supplementary Table 13. Differences in BCIPHPP concentrations between the different countries. A Kruskal-Wallis test with adjusted p-values for pairwise comparisons was performed with $p \leq 0.05$ for the adjusted p-value considered significant.

BCIPHPP	Bangladesh	Egypt	Indonesia	South Korea	Thailand
Bangladesh		1.000	<u>< 0.001*</u>	<u>< 0.001*</u>	<u>< 0.001*</u>
Egypt			<u>< 0.001*</u>	<u>< 0.001*</u>	<u>< 0.001*</u>
Indonesia				<u>0.002*</u>	<u>0.001*</u>
South Korea					<u>< 0.001*</u>
Thailand					

Significant values are underlined and indicated with an asterisk.

Supplementary Table 14. Differences in EHPHP concentrations between the different countries. A Kruskal-Wallis test with adjusted p-values for pairwise comparisons was performed with $p \leq 0.05$ for the adjusted p-value considered significant.

EHPHP	Bangladesh	Egypt	Indonesia	South Korea	Thailand
Bangladesh		<u>$\leq 0.001^*$</u>	<u>0.001^*</u>	<u>$\leq 0.001^*$</u>	<u>$\leq 0.001^*$</u>
Egypt			0.663	1.000	1.000
Indonesia				<u>0.034^*</u>	1.000
South Korea					0.120
Thailand					

Significant values are underlined and indicated with an asterisk.

Supplementary Table 15. Differences in 5-HO-EHDPHP concentrations between the different countries. A Kruskal-Wallis test with adjusted p-values for pairwise comparisons was performed with $p \leq 0.05$ for the adjusted p-value considered significant.

5-HO-EHDPHP	Bangladesh	Egypt	Indonesia	South Korea	Thailand
Bangladesh		<u>$\leq 0.001^*$</u>	<u>$\leq 0.001^*$</u>	<u>$\leq 0.001^*$</u>	<u>$\leq 0.001^*$</u>
Egypt			<u>$\leq 0.001^*$</u>	1.000	1.000
Indonesia				<u>$\leq 0.001^*$</u>	<u>$\leq 0.001^*$</u>
South Korea					1.000
Thailand					

Significant values are underlined and indicated with an asterisk.

Supplementary Table 16. Results of multivariate analysis for the identification of PFR metabolite exposure determinants taking into account samples from all five countries. Variables showing a significance of $p \leq 0.05$ were kept in the final model. Age, sex and specific gravity were always kept in the model as a priori confounders.

Compound	R ²	Variable	n	Categories	e ^B (95% CI)	p-value
DHPH	0.191	Country (p < 0.001)	85	Bangladesh	0.62 (0.48-0.80)	< 0.001
			84	Egypt	1.17 (0.92-1.48)	0.190
			90	Indonesia	0.71 (0.54-0.92)	0.009
			88	South Korea	1.71 (1.31-2.23)	< 0.001
			102	Thailand	reference	
BDCIPP	0.176	Country (p < 0.001)	85	Bangladesh	0.81 (0.63-1.05)	0.113
			68	Egypt	0.72 (0.56-0.92)	0.010
			90	Indonesia	0.64 (0.49-0.83)	< 0.001
			86	South Korea	1.38 (1.05-1.81)	0.019
			100	Thailand	reference	
BCIPHIPP	0.368	Hip circumference (p = 0.0030)	429		0.99 (0.98-1.00)	0.003
		Country (p < 0.001)	85	Bangladesh	0.41 (0.30-0.57)	< 0.001
			68	Egypt	0.41 (0.30-0.56)	< 0.001
			90	Indonesia	2.35 (1.68-3.28)	< 0.001
			86	South Korea	2.46 (1.75-3.47)	< 0.001
			100	Thailand	reference	
Sum EHDPHP	0.107	Country (p < 0.001)	429		1.02 (1.01-1.03)	< 0.001
			85	Bangladesh	0.65 (0.53-0.81)	< 0.001
			84	Egypt	1.05 (0.86-1.28)	0.624
			90	Indonesia	0.87 (0.70-1.08)	0.213
			88	South Korea	0.95 (0.76-1.19)	0.677
Sum PFRs	0.21	Country (p < 0.001)	102	Thailand	reference	
			85	Bangladesh	0.53 (0.42-0.67)	< 0.001
			84	Egypt	0.76 (0.61-0.94)	0.013
			90	Indonesia	0.99 (0.78-1.27)	0.963
			88	South Korea	1.58 (1.23-2.02)	< 0.001
			102	Thailand	reference	

Supplementary Table 17. Results of multivariate analysis for the identification of PFR metabolite exposure determinants taking into account samples from Egypt. Variables showing a significance of $p \leq 0.05$ were kept in the final model. Age, sex and specific gravity were always kept in the model as a priori confounders.

Compound	R ²	Variable	n	Categories	e ^B (95% CI)	p-value
DHPH	0.169	Frequency of consuming Koshary (p = 0.011)				
BDCIPP			36	Less than twice a week	0.51 (0.33-0.79)	0.003
			14	3-4 times a week	0.54 (0.31-0.94)	0.029
			19	5 times a week or more	reference	
BCIPHIPP	No significant variables					
Sum EHDPHP	No significant variables					
Sum PFRs	No significant variables					

Supplementary Table 18. Results of multivariate analysis for the identification of PFR metabolite exposure determinants taking into account samples from Bangladesh. Variables showing a significance of $p \leq 0.05$ were kept in the final model. Age, sex and specific gravity were always kept in the model as a priori confounders.

Compound	R	Variable	n	Categories	e ^B (95% CI)	p-value
DPHP	0.068	House renovated within last year (p = 0.008)	48	No	0.65 (0.47-0.89)	0.008
BDCIPP		No significant variables	37	Yes		
BCIPHIPP		No significant variables				
Sum PFRs		No significant variables				

*No multivariate analysis was performed for Σ EHPHP due to the low DF (< 50%) of these compounds in Bangladesh.

Supplementary Table 19. Results of multivariate analysis for the identification of PFR metabolite exposure determinants taking into account samples from Thailand. Variables showing a significance of $p \leq 0.05$ were kept in the final model. Age, sex and specific gravity were always kept in the model as a priori confounders.

Compound	R ²	Variable	n	Categories	e ^B (95% CI)	p-value
DPHP	0.074	Frequency of consuming fermented sauce during last year (p = 0.007)	58	Less than once a week	0.48 (0.31-0.76)	0.002
			25	1-4 times a week	0.59 (0.36-0.98)	0.042
			15	More than 4 times a week	reference	
BDCIPP	0.108	Hip circumference (p=0.016)	97		0.99 (0.98-1.00)	0.016
		Frequency of microwaving food with plasticware during last year (p = 0.027)	60	Never	0.67 (0.48-0.96)	0.027
			37	Yes	reference	
BCIPHIPP	0.154	Hip circumference (p < 0.001)	97		1.03 (1.01-1.05)	< 0.001
		Frequency of microwaving food with plastic wrap (p = 0.013)	66	Never	0.47 (0.26-0.85)	0.013
			31	Yes	reference	
Sum EHPHP	0.137	Frequency of storing food or drink with plastic wrap in refrigerator during last year (p=0.013)	51	Never	0.71 (0.54-0.94)	0.015
			26	Less than once a week	0.63 (0.46-0.87)	0.005
			21	Once a week or more	reference	
Sum PFRs	0.089	Frequency of drinking paper packed beverage during last year (p=0.016)	57	Never	0.57 (0.37-0.90)	0.016
			41	Yes	reference	
		Frequency of using plastic packages for eating food during last year (p=0.024)	41	Never	1.08 (0.62-1.88)	0.786
			35	Less than twice a week	0.59 (0.36-0.97)	0.037
			22	Twice a week or more	reference	

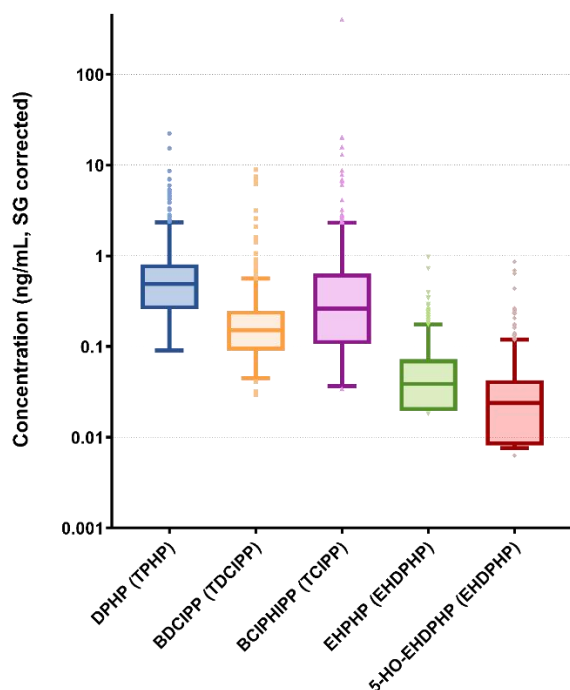
Supplementary Table 20. Results of multivariate analysis for the identification of PFR metabolite exposure determinants taking into account samples from Indonesia. Variables showing a significance of $p \leq 0.05$ were kept in the final model. Age, sex and specific gravity were always kept in the model as a priori confounders.

Compound	R ²	Variable	n	Categories	e ^B (95% CI)	p-value
DHPH	0.020	Frequency of consuming canned food during last year (p = 0.043)	50	Not consumed	0.69 (0.48-0.99)	0.043
			25	Consumed	reference	
BDCIPP	0.121	Frequency of eating ready meal during last year (p = 0.050)	29	Never	0.72 (0.50-1.05)	0.087
			31	Less than once a week	1.04 (0.68-1.12)	0.812
			18	Once a week or more	reference	
BCIPHIPP	0.028	Frequency of drinking canned beverage during last year (p = 0.039)	41	Less than once a week	0.64 (0.42-0.98)	0.039
			35	Once a week or more	reference	
Sum EHDPHP	0.010	Was house built within last 3 years (p = 0.015)	20	No	1.43 (1.02-2.01)	0.015
			70	Yes	reference	
Sum PFRs	0.041	Frequency of drinking canned beverage during last year (p = 0.014)	41	Less than once a week	0.70 (0.53-0.93)	0.014
			35	Once a week or more	reference	

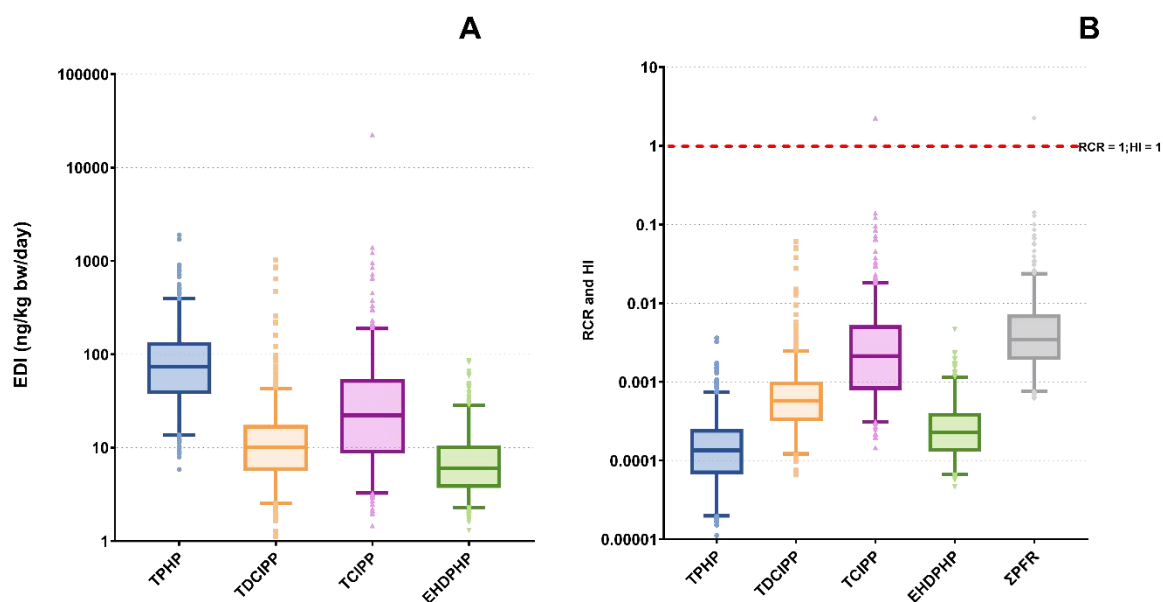
Supplementary Table 21. Results of multivariate analysis for the identification of PFR metabolite exposure determinants taking into account samples from South Korea. Variables showing a significance of $p \leq 0.05$ were kept in the final model. Age, sex and specific gravity were always kept in the model as a priori confounders.

Compound	R ²	Variable	n	Categories	e ^B (95% CI)	p-value
DHPH	0.034	Was house built within last 3 years (p = 0.007)	78	No	2.45 (1.29-4.64)	0.007
			10	Yes	reference	
		Frequency of microwaving food with plasticware during last year (p = 0.027)	27	Never	0.61 (0.39-0.94)	0.027
			61	Yes	reference	
BDCIPP	0.338	Frequency of eating ready meal during last year (p = 0.013)	3	Never	0.69 (0.37-1.28)	0.239
			33	Less than once a week	0.71 (0.56-0.90)	0.004
		Maternal education (p = 0.026)	52	Once a week or more	reference	
			19	High school	1.41 (0.91-2.18)	0.121
BCIPHIPP	0.088	Frequency of consuming eggs during last year (p = 0.011)	61	Undergraduate	0.96 (0.65-1.41)	0.816
			8	Graduate degree or higher	reference	
		Frequency of using humidifier during last 3 months (p = 0.034)	37	Less than twice a week	0.47 (0.27-0.84)	0.010
			40	3-4 times a week	0.43 (0.24-0.74)	0.003
Sum EHDPHP	0.221	Frequency of using humidifier during last 3 months (p = 0.034)	11	5-6 times a week or more	reference	
			74	Less than once a week	1.69 (1.04-2.73)	0.034
		Frequency of storing food or drink with plasticware in refrigerator during last year (p = 0.015)	14	Once a week or more	reference	
			27	Never	0.54 (0.38-0.82)	0.004
Sum PFRs	0.150	Frequency of storing food or drink with plasticware in refrigerator during last year (p = 0.015)	41	Less than once a week	0.70 (0.48-1.02)	0.063
			20	Once a week or more	reference	
		Frequency of air conditioner during the last 3 months (p = 0.039)	36	Less than once a week	0.73 (0.54-0.98)	0.039
			52	Once a week or more	reference	
		Frequency of consuming eggs during last year (p = 0.005)	37	Less than twice a week	0.54 (0.34-0.85)	0.008
			40	3-4 times a week	0.48 (0.31-0.74)	0.001
		Frequency of using humidifier during last 3 months (p = 0.020)	11	5-6 times a week or more	reference	
			74	Less than once a week	1.58 (1.08-2.31)	0.020
		Frequency of microwaving food with plasticware during last year (p = 0.028)	14	Once a week or more	reference	
			27	Never	0.71 (0.52-0.96)	0.028
		Was house built within last 3 years (p=0.039)	61	Yes	reference	
			78	No	1.58 (1.03-2.45)	0.039
			10	Yes	reference	

Supplementary Figures



Supplementary Figure 1. Median concentrations of PFR metabolites detected in more than 50% of urine samples from all 5 countries. Displayed concentrations are corrected for specific gravity, the y-axis is displayed on a logarithmic scale with the parent compound displayed between brackets. Median and IQRs are represented by the box, while the whiskers represent 5% and 95% percentiles with data points outside this range plotted individually.



Supplementary Figure 2. Estimated daily intakes (EDI in ng/kg bw/day) (A) and risk characterization ratio (RCR) for individual PFRs with the hazard index (HI) for the sum of PFRs (B) for samples from all countries. Median and IQRs are represented by the box, while the whiskers represent 5% and 95% percentiles with data points outside this range plotted individually.

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