

Supplementary Material

Occurrence of artificial sweeteners in human liver and paired blood and urine from adults in

Tianjin, China and their implications for human exposure

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Standards and reagents

Native standards: saccharin (SAC, $\geq 99\%$), cyclamate (CYC, $\geq 99\%$), and acesulfame (ACE, $\geq 99\%$) were purchased from Sigma-Aldrich (St. Louis, MO, USA); neotame (NEO, $\geq 98\%$) was acquired from USP Reference Standards (Rockville, MD, USA); and aspartame (ASP, analytical standard) was obtained from Supelco (Bellefonte, PA, USA). Internal standards: ACE-d₄ and ASP-d₅ were obtained from TRC (North York, ON, Canada). The structures and selected properties of investigated ASs in present study are shown in **Table S1**.

All other solvents and reagents were of HPLC or analytical grade. Methyl tert-butyl ether (MTBE) and methanol were purchased from Dima Technology Inc (Richmond Hill, ON, USA). Sodium carbonate, sodium bicarbonate, ammonium acetate, ammonium hydroxide, tris (hydroxymethyl) aminomethane (TRIS) and tetrabutyl ammonium hydrogen sulfate (TBAHS) used as ion-pair reagent were obtained from Aldrich (St Louis, MO, USA).

Oasis WAX extraction cartridges (3cc, 60 mg) were purchased from Waters Company (Milford, MA, USA). The Envi-carbon particle was obtained from Supelco (Bellefonte, PA, USA).

Sample extraction

Urine: approximately 20 mL of urine sample was transferred into a 50-mL PP-tube, and then spiked with 300 ng (30 μ L, 10 ng/ μ L) of each internal standard (ACE-d₄ and ASP-d₅). The spiked samples were extracted using Oasis WAX extraction cartridges (60 mg/3 cc). Prior to loading of the samples, the WAX cartridges were conditioned with 4 mL of 0.1% ammonium hydroxide in methanol, and 4 mL of milli-Q water. The samples were loaded on the conditioned cartridge at a rate of 3 mL/min. The cartridges were then washed with 4 mL of 25 mM sodium acetate buffer (pH = 4). Then, elutes was performed by shaking the slurry for 10 mins, and centrifugation at 3800 (\times g) for 8

mins. Finally, the extracted solutions were transferred into an autosampler vial for instrumental analysis.

Whole blood and liver: Prior to extraction, samples of whole blood were thawed and allowed to return to room temperature. One milliliter of blood sample (approximately 0.2 g of homogenized liver) was added to a 15 mL polypropylene (PP) tube, 10 ng of internal standards (ACE-d₄ and ASP-d₅, 100 µL, 0.10 ng/µL), 2.0 mL of 0.25 M sodium carbonate buffer and 1.0 mL of 0.5 M TBAHS (adjusted to pH 10) were added. After sufficient mixing, the extraction was carried out by the addition of 5 mL of MTBE, and the mixture was shaken vigorously for 40 mins. The organic layer were separated from the aqueous layer by centrifugation at 3800 (×g) for 5 mins and then transferred into a new 15 mL PP-tube. The extraction procedure was repeated with 3 mL of MTBE, the mixture was shaken vigorously for 20 mins and combined with the first fraction. The solvent was evaporated to near-dryness under a gentle stream of high-purity nitrogen and then reconstituted with 1.0 mL of methanol. After centrifugation at 3800 (×g) for 2 min, the solution were transferred into an autosampler vial for HPLC-MS/MS analysis.

Instrumental analysis

Separations were performed on an Agilent 1200 system (Agilent Technologies, USA) equipped with a CNW Athena C18-WP column (4.6 mm×150 mm, 3 µm) (CNW Technologies GmbH, Germany). The column was kept at 30°C. The mobile phase was composed of water (A) and acetonitrile (B), both containing 5 mM of ammonium acetate and 1 mM TRIS. Gradient elution was performed at a flow rate of 0.4 mL/min. The mobile phase gradient was ramped linearly from 0% to 75% B over 8 min, held for 1 min, returned back to 10% B over 1 min, ramped again to 70% B within 0.5 min, and held for 1.9 min. Eluent B was then lowered back to 0% within 0.5 min, and the

system was allowed to equilibrate for 8 min before the next injection. The injection volume was 20 μL , and injection was performed by an autosampler. Mass spectrometric analysis was performed using an Agilent 6410B Triple Quadrupole mass spectrometer (Agilent Technologies, USA) operated in negative ionization multiple-reaction monitoring (MRM) mode. Nitrogen (with a purity of 99.9%) was the desolvation gas with a manipulating temperature of 350°C. The flow rate was 10 L/min, and the nebulizing gas pressure was 50 psi. The capillary voltage was 4000 V. The dwell time was 200 ms. The mass transitions monitored were: 162 > 82.0 for ACE, 178.1 > 80.0 for CYC, 182.0 > 42.1 for SAC, 293.2 > 200.2 for ASP, 377.3 > 200.2 for NEO, 166.1 > 86.1 for ACE-d4, 298.3 > 205.2 for ASP-d5. When possible, multiple daughter ions were monitored for confirmation, but quantitation was based on a single product ion.

Table S1

Structures and selected properties of the five artificial sweeteners analyzed in this study.

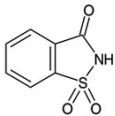
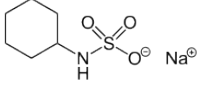
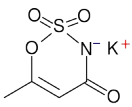
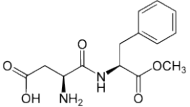
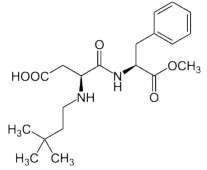
	Saccharin (SAC)	Cyclamate (CYC)	Acesulfame-K (ACE)	Aspartame (ASP)	Neotame (NEO)
CAS no.	81-07-2	139-05-9	33665-90-6	22839-47-0	165450-17-9
Structure					
Molecular formula	C ₇ H ₅ NO ₃ S	C ₆ H ₁₂ NaNO ₃ S	C ₄ H ₄ KNO ₄ S	C ₁₄ H ₁₈ N ₂ O ₅	C ₂₀ H ₃₀ N ₂ O ₅
Molecular weight (g/mol)	183.19	201.24	201.15	294.31	378.47
Log Kow	0.91	- 1.61	- 1.33	0.07	2.39
ADI (mg/kg bw/day)	5.0	7.0	9.0	40	2.0

Table S2
Characteristics of investigated participants.

variables	N ^a	range	mean	SD	median
<i>General adults (n = 54)</i>					
age (yrs)	54	22-62	43.2	10.2	47
BMI ^b (kg/m ²)	36	18.4-31.3	23.3	2.36	22.7
sex distribution	54	male: 29; female: 25			
age distribution	54	21-40 yrs: 17; 41-50 yrs: 17; 51-62 yrs: 20			
<i>Liver cancer patients (n = 11)</i>					
age (yrs)	11	39-80	59.5	13.1	58
Sex distribution	11	male: 7; female: 4			

^a total number may not be equal to the number of cases due to missing or unknown data.

^b BMI = Body Mass Index, BMI were calculated based on pre-delivery weight for pregnant women.

Table S3

Investigation on the usage of artificial sweeteners in six AS-containing food groups (i.e., pickles, preserved fruit, beverages, candies, condiments and puffed food) and one AS-containing living supply (i.e., commodities) selected from market in China ^a.

product groups	brand No.	Product No.	ACE	ASP	SAC	CYC	NEO	details
pickles (vegetable products)	B1	P1	✓ ^b	× ^c	×	✓	×	preserved mustard
		P2	✓	×	×	✓	×	enoki mushroom
		P3	✓	×	×	✓	×	bamboo shoot
	B2	P4	✓	×	✓	✓	×	preserved mustard
		P5	✓	×	✓	✓	×	enoki mushroom
		P6	✓	×	✓	✓	×	bamboo shoot
	B3	P7	✓	×	✓	✓	×	preserved mustard
		P8	✓	×	✓	✓	×	enoki mushroom
		P9	✓	×	✓	✓	×	bamboo shoot
	B4	P10	✓	×	×	×	×	preserved mustard
		P11	✓	×	×	×	×	enoki mushroom
		P12	✓	×	×	×	×	bamboo shoot
		P13	✓	×	×	×	×	radish
		P14	✓	×	×	×	×	pea
	B5	P15	✓	×	×	×	×	preserved mustard
		P16	✓	×	×	×	×	bamboo shoot
		P17	✓	×	×	×	×	radish
		P18	✓	×	×	×	×	pea
	B6	P19	✓	×	×	×	×	cabbage (mild)
		P20	✓	×	×	×	×	cabbage (moderate)
		P21	✓	×	×	×	×	cabbage (hot)
	B7	P22	✓	×	×	×	×	enoki mushroom
		P23	✓	×	×	×	×	pea
		P24	✓	×	×	×	×	leek
	B8	P25	✓	×	×	×	×	radish
		P26	✓	×	×	×	×	preserved mustard
		P27	✓	×	×	×	×	bamboo shoot
	B9	P28	✓	×	×	×	×	carrot
		P29	✓	×	×	×	×	radish
		P30	✓	×	×	×	×	bamboo shoot
	B10	P31	✓	×	×	×	×	kale borecole
		P32	✓	×	×	×	×	pea
		P33	✓	×	×	×	×	leek
	B11	P34	✓	×	×	×	×	kale borecole
		P35	✓	×	×	×	×	pea
		P36	✓	×	×	×	×	leek
	B12	P37	✓	×	×	×	×	kale borecole
		P38	✓	×	×	×	×	pea
	B13	P39	✓	×	×	×	×	preserved mustard
		P40	✓	×	×	×	×	radish
		P41	✓	×	×	×	×	pea
	B14	P42	✓	×	×	×	×	preserved mustard
		P43	✓	×	×	×	×	radish
	B15	P44	✓	×	×	×	×	pea
		P45	✓	×	×	×	×	preserved mustard

Table S2. Continue

product groups	brand No.	Product No.	ACE	ASP	SAC	CYC	NEO	details
preserved fruit	B16	P46	×	×	✓	✓	×	red bayberry
		P47	×	×	✓	✓	×	kiwi berry
		P48	×	×	✓	✓	×	orange
	B17	P49	×	✓	✓	✓	×	mango
		P50	×	✓	✓	✓	×	apple
		P51	×	✓	✓	✓	×	grape
	B18	P52	×	✓	✓	✓	×	orange
		P53	×	✓	✓	✓	×	mango
		P54	×	✓	✓	✓	×	apple
	B19	P55	×	×	✓	✓	×	hami melon
		P56	×	×	✓	✓	×	blueberry
		P57	×	×	✓	✓	×	durian
	B20	P58	×	✓	✓	✓	×	cumquat
		P59	×	✓	✓	✓	×	solanum tuberds
		P60	×	✓	✓	✓	×	mulberry
	B21	P61	×	×	✓	✓	×	red bayberry
		P62	×	×	✓	✓	×	plum candy
		P63	×	×	✓	✓	×	prune
		P64	×	×	✓	✓	×	green plum
		P65	×	×	✓	✓	×	dark plum
	B22	P66	×	×	✓	✓	×	red bayberry
		P67	×	×	✓	✓	×	plum candy
		P68	×	×	✓	✓	×	prune
		P69	×	×	✓	✓	×	green plum
		P70	×	×	✓	✓	×	dark plum
	B23	P71	×	✓	✓	✓	×	mango
		P72	×	✓	✓	✓	×	papaya
	B24	P73	×	✓	✓	✓	×	papaya
		P74	×	✓	✓	✓	×	prune
		P75	×	✓	✓	✓	×	green plum
		P76	×	✓	✓	✓	×	dark plum
	B25	P77	×	×	✓	✓	×	red bayberry
		P78	×	×	✓	✓	×	mango
		P79	×	×	✓	✓	×	papaya
	B26	P80	×	✓	×	×	×	banana
		P81	×	✓	×	×	×	grape
	B27	P82	×	✓	✓	✓	×	banana
		P83	×	✓	✓	✓	×	red bayberry
		P84	×	✓	✓	✓	×	mango
	B28	P85	×	✓	✓	✓	×	red bayberry
		P86	×	✓	✓	✓	×	plum candy
	B29	P87	×	✓	✓	✓	×	red bayberry
		P88	×	✓	✓	✓	×	plum candy
	B30	P89	×		✓	✓	×	red bayberry
		P90	×		✓	✓	×	plum candy
		P91	×		✓	✓	×	grape
	B31	P92	×	✓	✓	×	×	red bayberry
		P93	×	✓	✓	×	×	plum candy
		P94	×	✓	✓	×	×	grape

Table S2. Continue

product groups	brand No.	Product No.	ACE	ASP	SAC	CYC	NEO	details	
preserved fruit	B32	P95	×	✓	✓	✓	×	red bayberry	
		P96	×	✓	✓	✓	×	plum candy	
		P97	×	✓	✓	✓	×	grape	
	B33	P98	×	×	✓	×	✓	red bayberry	
		P99	×	×	✓	×	✓	plum candy	
		P100	×	×	✓	×	✓	grape	
	B34	P101	×	×	✓	✓	×	cocoa flavor	
		P102	×	×	✓	✓	×	red bayberry	
		P103	×	×	✓	✓	×	plum candy	
		P104	×	×	✓	✓	×	green plum	
	beverages	B35	P105	×	✓	×	×	×	apple flavor
			P106	×	✓	×	×	×	apple flavor (puried)
		B36	P107	✓	✓	×	×	×	orange flavor
			P108	✓	✓	×	×	×	strawberry
P109			✓	✓	×	×	×	watermelon flavor	
P110			✓	✓	×	×	×	grapefruit favor	
B37		P111	✓	✓	×	×	×	orange flavor	
		P112	✓	✓	×	×	×	strawberry	
		P113	✓	✓	×	×	×	watermelon flavor	
		P114	✓	✓	×	×	×	snow pear	
B38		P115	✓	✓	×	×	×	grapefruit favor	
		P116	✓	✓	×	×	×	orange flavor	
		P117	✓	✓	×	×	×	strawberry	
B39		P118	✓	×	×	×	×	watermelon flavor	
	P119	✓	×	×	×	×	orange flavor		
	P120	✓	×	×	×	×	strawberry		
B40	P121	✓	✓	×	×	×	orange flavor		
	P122	✓	✓	×	×	×	strawberry		
candies	B41	P123	✓	✓	×	×	×	chewing gum	
		P124	✓	✓	×	×	×	chewing gum	
		P125	✓	✓	×	×	×	chewing gum	
		P126	✓	✓	×	×	×	chewing gum	
		P127	✓	✓	×	×	×	chewing gum	
	B42	P128	✓	✓	×	×	×	chewing gum	
		P129	✓	✓	×	×	×	chewing gum	
		P130	✓	✓	×	×	×	chewing gum	
		P131	✓	✓	×	×	×	chewing gum	
	B43	P132	×	✓	×	×	×	chewing gum	
		P133	×	✓	×	×	×	chewing gum	
		P134	×	✓	×	×	×	chewing gum	
		P135	×	✓	×	×	×	chewing gum	
	B44	P136	✓	✓	×	×	×	chewing gum	
P137		✓	✓	×	×	×	chewing gum		
P138		✓	✓	×	×	×	chewing gum		
B45	P139	×	✓	×	×	×	chewing gum		
	P140	×	✓	×	×	×	chewing gum		
	P141	×	✓	×	×	×	chewing gum		
B46	P142	✓	✓	×	×	×	marshmallow (strawberry)		
	P143	✓	✓	×	×	×	marshmallow (mint)		

Table S2. Continue

product groups	brand No.	Product No.	ACE	ASP	SAC	CYC	NEO	details
candies	B47	P144	×	✓	×	×	×	marshmallow (strawberry)
		P145	×	✓	×	×	×	marshmallow (mint)
		P146	×	✓	×	×	×	marshmallow (mustard)
	B48	P147	×	✓	×	×	×	marshmallow (orange)
		P148	×	✓	×	×	×	soy milk (strawberry)
		P149	×	✓	×	×	×	soy milk (orange)
condiments	B49	P150	×	✓	×	×	×	soy milk (cocoa)
		P151	✓	×	×	×	×	light soy sauce
		P152	✓	×	×	×	×	dark soy sauce
	B50	P153	✓	×	×	×	×	super soy sauce
		P154	✓	✓	×	×	×	light soy sauce (510 mL)
		P155	✓	✓	×	×	×	light soy sauce (1.9 L)
		P156	✓	✓	×	×	×	dark soy sauce
		P157	✓	✓	×	×	×	super soy sauce
	B51	P158	✓	×	×	×	×	light soy sauce
		P159	✓	×	×	×	×	dark soy sauce (560 mL)
		P160	✓	×	×	×	×	super soy sauce
	B52	P161	✓	×	×	×	×	dark soy sauce (2.5 L)
		P162	✓	×	×	×	×	light soy sauce
		P163	✓	×	×	×	×	dark soy sauce
	B53	P164	✓	×	×	×	×	super soy sauce
		P165	✓	✓	×	×	×	light soy sauce
		P166	✓	✓	×	×	×	dark soy sauce
	B54	P167	✓	✓	×	×	×	super soy sauce
		P168	✓	×	×	×	×	light soy sauce
		P169	✓	×	×	×	×	dark soy sauce
	B55	P170	✓	×	×	×	×	super soy sauce
		P171	✓	✓	×	×	×	light soy sauce
		P172	✓	✓	×	×	×	dark soy sauce
	B56	P173	✓	✓	×	×	×	super soy sauce
		P174	✓	×	×	×	×	light soy sauce
		P175	✓	×	×	×	×	dark soy sauce
	B57	P176	✓	×	×	×	×	super soy sauce
P177		✓	×	×	×	×	light soy sauce	
P178		✓	×	×	×	×	dark soy sauce	
B58	P179	✓	✓	×	×	×	super soy sauce	
	P180	✓	✓	×	×	×	light soy sauce	
	P181	✓	✓	×	×	×	dark soy sauce	
B59	P182	✓	×	×	×	×	sweet chili sauce	
	P183	✓	×	×	×	×	sweet chili sauce	
B60	P184	✓	×	×	×	×	sweet chili sauce	
	P185	✓	×	×	×	×	tomato sauce (220 g)	
puffed food	B61	P186	✓	×	×	×	×	tomato sauce (340 g)
		P187	×	✓	×	×	×	lime flavor
		P188	×	✓	×	×	×	red meat flavor
	B62	P189	×	✓	×	×	×	cucumber flavor
		P190	×	✓	×	×	×	numb&spicy flavor
		P191	×	✓	×	×	×	red meat flavor
		P192	×	✓	×	×	×	cucumber flavor
		P193	×	✓	×	×	×	numb&spicy flavor

Table S2. Continue

product groups	brand No.	Product No.	ACE	ASP	SAC	CYC	NEO	details
puffed food	B63	P194	×	✓	×	×	×	tomato flavor
		P195	×	✓	×	×	×	lime flavor
	B64	P196	×	✓	×	×	×	tomato flavor
		P197	×	✓	×	×	×	lime flavor
	B65	P198	×	✓	×	×	×	cucumber
		P199	×	✓	×	×	×	red meat flavor
P200		×	✓	×	×	×	lime flavor	
commodities	B66	P201	×	×	✓	×	×	mouthwash (green tea)
		P202	×	×	✓	×	×	mouthwash (mint)
	B67	P203	×	×	✓	×	×	mouthwash (light)
		P204	×	×	✓	×	×	mouthwash (heavy)
	B68	P205	×	×	✓	×	×	mouthwash (light)
		P206	×	×	✓	×	×	mouthwash (heavy)
	B69	P207	×	×	✓	×	×	mouthwash (light)
		P208	×	×	✓	×	×	mouthwash (heavy)
	B70	P209	×	×	✓	×	×	mouthwash (light)
		P210	×	×	✓	×	×	mouthwash (heavy)
		B71	P211	×	×	✓	×	×
	P212		×	×	✓	×	×	toothpaste for children (strawberry)
	P213		×	×	✓	×	×	toothpaste for children (apple)
	B72	P214	×	×	✓	×	×	toothpaste for children (orange)
		P215	×	×	✓	×	×	toothpaste for children (strawberry)
		P216	×	×	✓	×	×	toothpaste for children (fruit)
	B73	P217	×	×	✓	×	×	toothpaste for children (orange)
		P218	×	×	✓	×	×	toothpaste for children (mint)
		P219	×	×	✓	×	×	toothpaste for children (banana)
	B74	P220	×	×	✓	×	×	toothpaste for children (orange)
		P221	×	×	✓	×	×	toothpaste for children (strawberry)
		P222	×	×	✓	×	×	toothpaste for children (apple)
	B75	P223	×	×	✓	×	×	toothpaste for children (orange)
		P224	×	×	✓	×	×	toothpaste for children (strawberry)
		P225	×	×	✓	×	×	toothpaste for children (banana)
	B76	P226	×	×	✓	×	×	toothpaste for children (apple)
		P227	×	×	✓	×	×	toothpaste for children (strawberry)
		P228	×	×	✓	×	×	toothpaste for children (orange)
	B77	P229	×	×	✓	×	×	toothpaste for children (orange)
		P230	×	×	✓	×	×	toothpaste for children (strawberry)
		P231	×	×	✓	×	×	toothpaste for children (apple)
	B78	P232	×	×	✓	×	×	toothpaste for children (orange)
		P233	×	×	✓	×	×	toothpaste for children (strawberry)
		P234	×	×	✓	×	×	toothpaste for children (apple)
	B79	P235	×	×	✓	×	×	toothpaste for children (orange)
		P236	×	×	✓	×	×	toothpaste for children (strawberry)
		P237	×	×	✓	×	×	toothpaste for children (apple)
	B80	P238	×	×	✓	×	×	toothpaste for adults (efficacy#1)
		P239	×	×	✓	×	×	toothpaste for adults (efficacy#2)
		P240	×	×	✓	×	×	toothpaste for adults (efficacy#3)
	B81	P241	×	×	✓	×	×	toothpaste for adults (efficacy#1)
		P242	×	×	✓	×	×	toothpaste for adults (efficacy#2)
P243		×	×	✓	×	×	toothpaste for adults (efficacy#3)	

Table S2. Continue

product groups	brand No.	Product No.	ACE	ASP	SAC	CYC	NEO	details
commodities	B82	P244	×	×	✓	×	×	toothpaste for adults (efficacy#1)
		P245	×	×	✓	×	×	toothpaste for adults (efficacy#2)
		P246	×	×	✓	×	×	toothpaste for adults (efficacy#3)
	B83	P247	×	×	✓	×	×	toothpaste for adults (efficacy#1)
		P248	×	×	✓	×	×	toothpaste for adults (efficacy#2)
		P249	×	×	✓	×	×	toothpaste for adults (efficacy#3)
	B84	P250	×	×	✓	×	×	toothpaste for adults (efficacy#1)
		P251	×	×	✓	×	×	toothpaste for adults (efficacy#2)
		P252	×	×	✓	×	×	toothpaste for adults (efficacy#3)
	B85	P253	×	×	✓	×	×	toothpaste for adults (efficacy#1)
		P254	×	×	✓	×	×	toothpaste for adults (efficacy#2)
		P255	×	×	✓	×	×	toothpaste for adults (efficacy#3)
	B86	P256	×	×	✓	×	×	toothpaste for adults (efficacy#1)
		P257	×	×	✓	×	×	toothpaste for adults (efficacy#2)
		P258	×	×	✓	×	×	toothpaste for adults (efficacy#3)
	B87	P259	×	×	✓	×	×	toothpaste for adults (efficacy#1)
		P260	×	×	✓	×	×	toothpaste for adults (efficacy#2)
		P261	×	×	✓	×	×	toothpaste for adults (efficacy#3)

^a These information comes from ingredient lists

^b ✓ = product contains this AS.

^c × = product does not contains this AS.

Table S4Distribution of each AS in food products and living supplies investigated in China ^a.

	ACE	ASP	SAC	CYC	NEO
all (<i>n</i> ^b = 261)	111	100	124	60	3
pickles (<i>n</i> = 45)	45	0	6	9	0
preserved fruit (<i>n</i> = 59)	0	30	57	51	3
beverages (<i>n</i> = 18)	16	15	0	0	0
candies (<i>n</i> = 28)	14	28	0	0	0
condiments (<i>n</i> = 36)	36	13	0	0	0
puffed food (<i>n</i> = 14)	0	14	0	0	0
commodities (<i>n</i> = 61)	0	0	61	0	0

^a the number of investigated products containing this AS is shown in corresponding blank.^b the total of investigated products.

Table S5

Concentration ratios of SAC, CYC and ACE between blood and urine, and renal clearance rates and daily intake estimated for adults in China ^a.

	PB/PU ratio				renal clearance (mL/day/kg)				daily intake ($\mu\text{g}/\text{kg}$ bw/day)			
	mean	median	min ^b	max ^c	mean	median	min	max	mean	median	min	max
SAC	1.06	0.16	0.002	22.3	1300	154	1.10	14,000	9.27	1.72	0.07	67.5
CYC	0.017	0.004	< 0.001	0.23	16,500	5,480	94.8	180,000	NA ^d	NA	NA	NA
ACE	0.046	0.005	< 0.001	0.34	10,700	4,810	64.4	60,000	33.8	4.61	0.05	229

^a We calculated the PB/PU ratio, renal clearance and daily intake of ASs when all data set were analyzed collectively.

^b min = minimum value.

^c max = maximum value.

^d NA = not available, CYC is metabolized in humans, therefore, urinary level can not be used for the estimation of human CYC exposure dose.

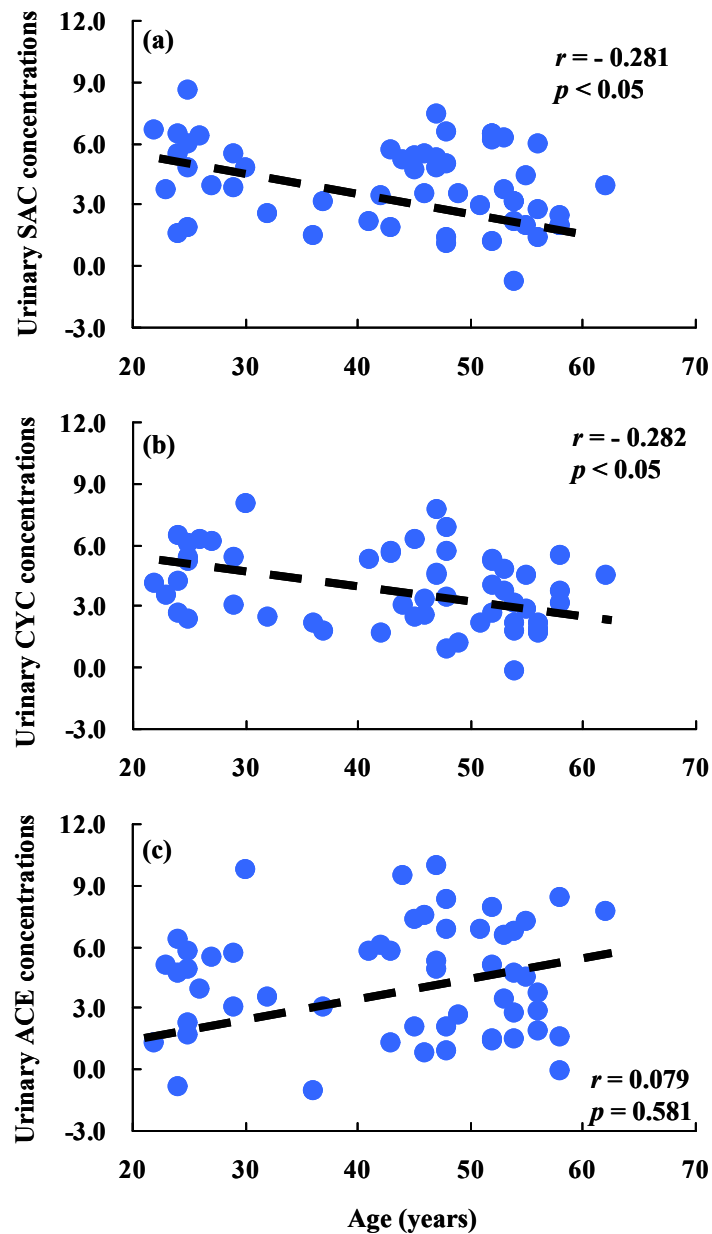


Fig. S1. Relationships of creatinine-adjusted urinary SAC, CYC and ACE concentrations with age of donors from Tianjin, China. All concentration values which lower than LOQ were excluded from these analysis; while outliers were included due to that log-transformation concentrations were used for these analyses.

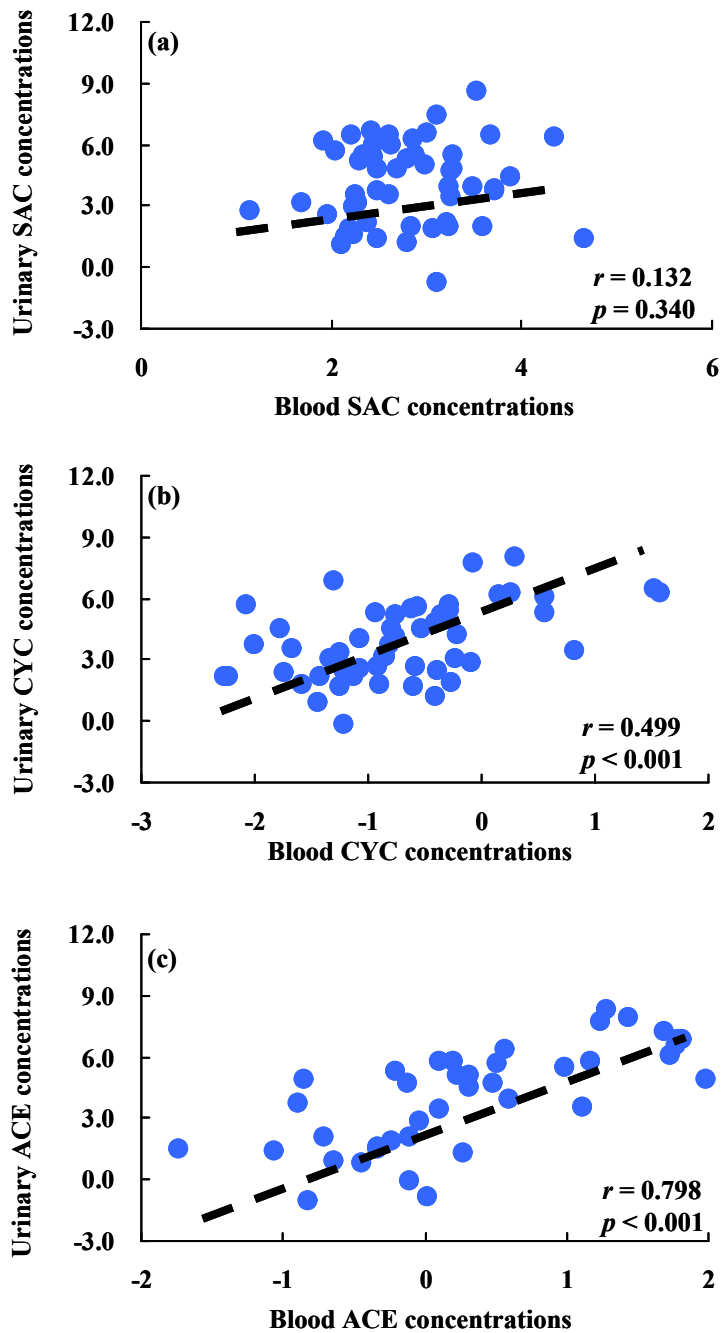


Fig. S2. Relationships of individual AS concentrations between urine (creatinine-adjusted) and blood. Plot (a), (b) and (c) represent associations for SAC, CYC, and ACE, respectively; all concentration values which lower than LOQ were excluded from these analysis; while outliers were included due to that log-transformation concentrations were used for these analyses.