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双酚类化合物污染现状及对生命早期的不良影响

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摘要：双酚类化合物广泛应用于日用品生产。本研究首先综述双酚类化合物的污染现状,发现其在多个国家的室内灰尘、地表水、饮用水处理厂水源、污水处理厂污泥和沉积物等环境介质、食物尤其是罐装食品和饮料甚至尿液、血液、胎盘、母乳、羊水、脑组织、头发和脂肪等人体样本中均有检出,主要为双酚 A、双酚 S、双酚 F 和双酚 AF。相比成年人,胎儿和儿童接触更多的双酚类化合物,且对暴露更为敏感。本文从生殖毒性、神经毒性、呼吸和免疫毒性、致肥胖效应和发育毒性等方面综述生命早期接触双酚类化合物产生的不良影响,发现双酚 S、双酚 F 等双酚 A 替代物具有与双酚 A 相似的毒性效应。最后,从检测方法标准化、加强环境流行病学研究等方面对今后的研究进行了展望。

关键词：双酚类化合物;污染现状;生命早期;不良影响
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Pollution Status and Adverse Effects of Bisphenols on Early Life

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Abstract：Bisphenols are extensively used in the products of daily necessities. In the present study, firstly, we summarized the pollution status of bisphenols, and found that, bisphenols including bisphenol A, bisphenol S, bisphenol F, and bisphenol AF were detected in indoor dust, surface water, source water of drinking water treatment plant, sludge of sewage treatment plant, sediment, food especially canned food and beverages, even in human samples such as urine, blood, placenta, breast milk, amniotic fluid, brain tissue, hair and adipose tissue in many countries. Compared with adults, fetuses and children are exposed to more bisphenols and more sensitive to bisphenols. We also investigated the adverse effects of early life exposure to bisphenols, including toxicities to reproductive, nervous, respiratory, immune, developmental system and obesogenic effects. Our study showed that toxicities of bisphenol A analogues such as bisphenol S and bisphenol F were similar to that of bisphenol A. Further, we provided the prospect on future researches in terms of standardization of detection methods and development of environmental epidemiology.

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Keywords: bisphenols; pollution status; early life; adverse effects

双酚 A(bisphenol A, BPA)是全球产量最高的产品之一,主要用于环氧树脂和聚碳酸酯的生产,应用于制造水杯、补牙材料、食品接触材料、涂料、管道和热敏纸等日用品[1]。体外分析和实验动物研究证明了 BPA 对生殖和发育、神经网络、心血管、代谢和免疫系统有不良影响[1-5],是一种环境内分泌干扰物(environmental endocrine disruptors, EEDs),被各国限制使用。因此,近年来双酚 AF (bisphenol AF, BPAF)、双酚 AP (bisphenol AP, BPAP)、双酚 B (bisphenol B, BPB)、双酚 F (bisphenol F, BPF)、双酚 P (bisphenol P, BPP)、双酚 S (bisphenol S, BPS)和双酚 Z (bisphenol Z, BPZ)等 BPA 类似物作为替代品得以广泛使用。欧洲化工局报告显示,欧洲经济区 BPF 和 BPS 年生产量或进口量分别高达 1 000 万 t 和 10 000 万 t[6]。在很多国家或地区,目前尚缺少双酚类化合物生产和使用的详细数据,但可以肯定的是,除 BPA 外,其他双酚类化合物(BPA 类似物)的生产和应用在全球范围内都在增加[7-8]。

双酚类化合物是半持久性有机污染物,正辛醇-水分配系数和生物富集因子较高,易在生物体内蓄积,毒性效应较强[7]。相比成年人,胎儿和儿童接触双酚类化合物更多,且对暴露更为敏感。本研究首先综述双酚类化合物在环境介质、食品和人体中的污染现状,然后从生殖毒性、神经毒性、呼吸和免疫毒性、致肥胖效应和发育毒性等方面综述生命早期接触双酚类化合物产生的不良影响,为双酚类化合物特别是双酚 A 替代物环境质量标准制定与污染控制提供数据支撑,为提高出生人口质量、保障儿童健康提供科学依据。

1　双酚类化合物污染现状(Pollution status of bisphenols)

1.1　在环境介质中的分布

归纳总结了双酚类化合物在灰尘、水体、污泥和沉积物等环境介质中的检出浓度范围,如表 1 所示。迄今为止,BPA、BPAF、BPAP、BPB、BPF、BPP、BPS 和 BPZ 等双酚类化合物在环境中有检出。

灰尘:在中国[9-11]、美国[10]、日本[10]、韩国[10]和瑞典[12]等国家的室内灰尘中,双酚类化合物均有检出。2017—2019 年,我国灰尘中 BPA 最高检出浓度高达 37 000 $ng \cdot g^{-1}$[9],与韩国相近(39.1 $\mu g \cdot g^{-1}$)[10],高于其他国家。

水体:在我国水体中,BPA、BPS 和 BPAF 是检出率和检出浓度较高的双酚类化合物。2017 年,我国 20 个饮用水处理厂水源中 BPA 浓度最高,可达 34.9 $ng \cdot L^{-1}$,BPS 检出范围为 n.d. ~ 5.2 $ng \cdot L^{-1}$[13]。辽河、浑河和太湖水体中 BPA、BPS 和 BPAF 检出率高达 100%,其中 BPS 浓度最高(0.28 ~ 67 $ng \cdot L^{-1}$)[14]。均未超过欧盟推荐的 BPA 预测无效应浓度(predicted no-effect concentration, PNEC) 1 500 $ng \cdot L^{-1}$[7]。

污泥:在中国[15]、韩国[16]和美国[17]等国家的污泥中也检测出了双酚类化合物。在韩国几类污水处理厂的污泥样品中双酚类化合物平均浓度依次为:BPA (1 520 $ng \cdot g^{-1}$)、BPF (384 $ng \cdot g^{-1}$)、BPS (44.9 $ng \cdot g^{-1}$)和 BPZ (24.3 $ng \cdot g^{-1}$),BPB 未检出,推测主要来源于工业排放[16]。在我国城市污水处理厂的污泥中,8 种双酚类化合物均有检出,检出率和检出浓度均表明 BPA 仍然是最主要的双酚类化合物,BPA 范围为 16.7 ~ 1 210 $ng \cdot g^{-1}$,BPA、BPF 和 BPS 的检出率分别为 100%、95.7% 和 89.1%[15]。

沉积物:双酚类化合物在中国[14]、美国[18]、韩国[18]和日本[18]临近工业区的湖泊和河流沉积物中也有检出,韩国沉积物 BPA 的检出浓度最高(范围为 n.d. ~ 13 700 $ng \cdot g^{-1}$),BPP 未检出,美国与日本仅有 BPA、BPF 和 BPS 检出[18]。在我国太湖流域沉积物中 BPS (0.28 ~ 69 $ng \cdot L^{-1}$)的浓度高于 BPA (0.19 ~ 7.4 $ng \cdot L^{-1}$)[14]。

1.2　在食品中的分布

饮食是人们摄入双酚类化合物的主要途径[19-20]。用于食品接触材料或食品加工塑料的双酚类化合物可以转移到食品中[20]。摄入罐装食品和饮料与体内 BPA 浓度较高有关[21-22],坚持新鲜食品饮食则相反[23-24]。最近的研究也报道了来自不同国家的食品中含有 BPA 类似物(表 2)。

在美国开展的一项包括饮料、乳制品、油脂、鱼和海鲜、肉类、谷物、水果和蔬菜的调查发现,美国食品中 BPA 和 BPF 的平均浓度分别为 3 $ng \cdot g^{-1}$ 和 0.929 $ng \cdot g^{-1}$,罐头食品比玻璃、纸或塑料容器中出售的食品含有更高浓度的单个和总双酚类化合物,统计分析时纳入罐头食品导致蔬菜中 BPA 浓度较高(9.97 $ng \cdot g^{-1}$)、海鲜中 BPF 浓度较高(4.63 $ng \cdot g^{-1}$)[25]。BPS 在我国食品样品中被检出(检出率为

77.5%);BPA 的检出率高达 60.9%,其浓度范围从<LOD 到 299 $ng \cdot g^{-1}$(平均浓度为 4.94 $ng \cdot g^{-1}$);其中,饮料中 BPA 浓度最高(平均浓度为 15.5 $ng \cdot g^{-1}$),其次是鱼和海鲜(14.1 $ng \cdot g^{-1}$)、水果(7.76 $ng \cdot g^{-1}$)和调味品(7.19 $ng \cdot g^{-1}$)[26]。意大利番茄罐头中 BPA、BPB 浓度(平均值)分别高达 19.62 $ng \cdot g^{-1}$、8.85 $ng \cdot g^{-1}$[27],高于前 2 项在美国、中国开展的调查研究[25-26]。在瑞典的芥末酱中 BPF 平均浓度为 1.85 $mg \cdot kg^{-1}$[28]。

1.3 在人体中的分布

由于双酚类化合物的广泛使用,人们通过摄入、呼吸和皮肤接触双酚类化合物,目前在人的尿液、血液、胎盘、母乳、羊水、脑组织、头发和脂肪中均有检出(表 3)。一项韩国研究报告了在孕妇尿液、新生儿尿液、胎盘和母乳标本中 BPA 检出率分别为 90.2%、82.2%、82.1% 和 79.5%,不同样本中 BPA 中位浓度依次为新生儿尿液(4.75 $\mu g \cdot L^{-1}$)、孕妇尿液(2.86 $\mu g \cdot L^{-1}$)、脐带血清(1.71 $\mu g \cdot L^{-1}$)、孕妇血清(1.56 $\mu g \cdot L^{-1}$)、母乳(0.74 $\mu g \cdot L^{-1}$)和胎盘(0.53 $\mu g \cdot kg^{-1}$)[29]。居住在中国电子拆解厂附近的孕妇和新生儿体内检出 5 种双酚类化合物,包括 BPA、BPS、BPAF、BPP 和 BPAP[30]。BPA 是德国儿童尿液中最主要的双酚类物质,几乎所有样本中均可检出(检出率 96%),中位数浓度高达 1.82 $\mu g \cdot L^{-1}$[31]。中国南京郊区儿童尿液中 BPA 和 BPS 检出率和检出浓度最高,检出率分别为 97.5% 和 98.8%,检出浓度中位值分别为 369 $ng \cdot L^{-1}$ 和 18.8 $ng \cdot L^{-1}$[32]。在另外 3 项研究中,BPF 超过 BPS 成为 BPA 的主要替代物,中国成年人体内 BPF 检出率是 BPS 的 3 倍左右(74.6% vs. 25.9%)[33],挪威儿童体内 BPF 检出率超过了 BPA (97% vs. 86%)[34],日本儿童体内 BPF 检出率高于 BPS (83% vs. 78%)[35]。

此外,在欧洲成年人的脑组织(下丘脑和白质)、头发和脂肪组织中均有 BPA 检出:荷兰成年人下丘脑和白质中,BPA 检出率分别为 96% 和 90%,浓度中位值分别为 0.68 $ng \cdot g^{-1}$ 和 0.82 $ng \cdot g^{-1}$[36];希腊孕妇的头发中 BPS 的检出率(34%)与 BPA 相近(37%)[37];42.9% 的西班牙成人脂肪组织中检出 BPA[38]。

值得一提的是,上述研究的健康风险评价结果表明,危害商值(hazard quotient, HQ) (评估每种双酚类化合物单独暴露对人体的健康风险)或危害指数(hazard index, HI) (评估多种双酚类化合物联合暴露的累积健康风险)均<1,即双酚类化合物估计每日摄入量(estimated daily intake, EDI)未超过欧洲食品安全局规定的 BPA 每日允许摄入量(tolerable daily intake, TDI)。

2 生命早期接触双酚类化合物的不良影响(Adverse effects of early life exposure to bisphenols)

越来越多的研究表明,妊娠期、婴儿期和幼儿期的环境压力源是儿童期甚至成年期疾病的危险因素[39-40]。对生命早期的干扰,会增加数年或数十年后出现不良健康结果的风险[39-40]。相比成人,胎儿和儿童更容易受到 EEDs 的影响。原因一:饮食、行为、生理、解剖和毒理动力学方面的差异[41],胎儿和儿童消耗水和特定食物更多,肠道吸收率、肠道表面积与体积比更高[42],接触双酚类化合物更多;原因二:生命早期机体处于生长发育阶段,代谢解毒机制尚不完善,对外界环境干扰比成年期更敏感[43]。

2.1 生殖毒性

早在 1979 年,Henderson 等[44]提出假说:在睾丸分化时雌激素相对过量是睾丸癌的主要危险因素。14 年后,Sharpe 和 Skakkebaek[45]提出,不仅睾丸癌,其他男性生殖障碍如隐睾、尿道下裂、低精子数量可能共享这一假说,接触具有类雌激素效应的环境化学品可能对男性生殖障碍发生起关键作用,潜在机制是胎儿垂体负反馈的增加导致促性腺激素水平降低,从而破坏男性胎儿性腺正常发育。

实验动物学研究中,围产期 SD 大鼠口服 BPA、BPS 和 BPF 后,5 $\mu g \cdot kg^{-1}$ BPA 使雌性后代卵泡数量、雄性后代肾脏和前列腺质量增加,诱导睾丸氧化应激反应;5 $\mu g \cdot kg^{-1}$ BPS 使雌性后代排卵率和雄性后代肛门—生殖器距离降低,诱导睾丸氧化应激反应;5 $\mu g \cdot kg^{-1}$ BPF 导致超过 80% 大鼠自然流产,雌性后代排卵率和雄性后代附睾脂肪组织质量降低,表明即使低剂量 BPA 或其类似物也会引起生殖毒性[46]。围产期暴露于高剂量 BPA,其雌性子代成年期发情周期模式发生改变,血浆促黄体生成素水平降低[47]。2 项 Wistar 大鼠的研究表明,出生后短时间暴露于超过 100 $mg \cdot kg^{-1}$ 的 BPF 可增加雌性子宫相对质量,更高剂量(500 $mg \cdot kg^{-1}$) BPF 暴露导致雄性睾丸质量增加[48-49]。发育早期(自妊娠第 8 天至产后第 19 天)低剂量 BPS (200 $\mu g \cdot kg^{-1} \cdot d^{-1}$)暴露可影响 CD-1 小鼠子宫和卵巢中雌激素应答基因表达,促进雌性后代卵巢卵泡发育[4]。

表 1　双酚类化合物在环境介质中的检出浓度范围

Table 1　Range of bisphenols concentrations in the environment

样本 Sample	国家 Country	单位 Unit	BPA	BPAF	BPAP	BPB	BPF	BPP	BPS	BPZ	参考文献 Reference
灰尘 Dust	中国 China	$ng \cdot g^{-1}$	n.d. ~ 37 000	n.d. ~ 52.3	n.d. ~ 73.2	n.d. ~ 42.3	n.d. ~ 10.11	n.d. ~ 18.4	n.d. ~ 1 880	n.d. ~ 366	[9]
灰尘 Dust	美国 United States	$\mu g \cdot g^{-1}$	0.20 ~ 9.38	n.d.	n.d. ~ 0.0071	n.d.	n.d. ~ 0.24	n.d.	0.0056 ~ 25.5	n.d.	[10]
	中国 China		n.d. ~ 8.35	n.d.	n.d.	n.d. ~ 0.03	n.d. ~ 1.89	n.d. ~ 0.63	0.00083 ~ 12.6	n.d.	
	日本 Japan		0.50 ~ 21.8	n.d. ~ 0.011	n.d.	n.d.	n.d. ~ 2.78	n.d.	0.25 ~ 2.55	n.d.	
	韩国 South Korea		0.98 ~ 39.1	n.d. ~ 0.091	n.d.	n.d.	n.d. ~ 107	n.d.	0.090 ~ 26.6	n.d.	
灰尘 Dust	中国 China	$\mu g \cdot g^{-1}$	0.54 ~ 26.2		n.d.	n.d.	0.02 ~ 2.37	n.d.	0.07 ~ 11.5	n.d.	[11]
灰尘 Dust	瑞典 Sweden	$\mu g \cdot g^{-1}$	n.d. ~ 15	n.d. ~ 2.8			n.d. ~ 15		n.d. ~ 22		[12]
水体 Water	中国 China	$ng \cdot L^{-1}$	n.d. ~ 34.9	n.d. ~ 10.8	n.d.	n.d. ~ 14.3	n.d. ~ 12.56	n.d.	n.d. ~ 5.2	n.d.	[13]
水体 Water	中国 China	$ng \cdot L^{-1}$	4.2 ~ 14	0.13 ~ 1.1	n.d. ~ 0.39	n.d.	n.d. ~ 5.6		0.28 ~ 67	n.d.	[14]
污泥 Sludge	中国 China	$ng \cdot g^{-1}$	16.7 ~ 1 210	n.d. ~ 140	n.d. ~ 16.3	n.d. ~ 3.55	n.d. ~ 245	n.d. ~ 13.5	n.d. ~ 19.7	n.d. ~ 16.3	[15]
污泥 Sludge	韩国 South Korea	$ng \cdot g^{-1}$	n.d. ~ 25 600	n.d. ~ 3.59	n.d. ~ 16.0	n.d.	n.d. ~ 1 780	n.d. ~ 26.2	n.d. ~ 523	n.d. ~ 969	[16]
污泥 Sludge	美国 United States	$ng \cdot g^{-1}$	6.48 ~ 4 700	n.d. ~ 72.2	n.d.	n.d. ~ 5.6	n.d. ~ 5.6	n.d. ~ 6.4	n.d. ~ 1 480	n.d. ~ 66.7	[17]
沉积物 Sediment	中国 China	$ng \cdot g^{-1}$	0.19 ~ 7.4	0.010 ~ 0.36	n.d. ~ 0.4	n.d.	n.d. ~ 1.2		n.d. ~ 0.76	n.d. ~ 2.5	[14]
沉积物 Sediment	美国 United States	$ng \cdot g^{-1}$	n.d. ~ 106	n.d.	n.d.	n.d.	n.d. ~ 27.5	n.d.	n.d. ~ 4.65	n.d.	[18]
	日本 Japan		1.88 ~ 23	n.d.	n.d.	n.d.	n.d. ~ 9.11	n.d.	n.d. ~ 4.46	n.d.	
	韩国 South Korea		n.d. ~ 13 370	n.d. ~ 4.23	n.d. ~ 252	n.d. ~ 10.6	n.d. ~ 9 650	n.d.	n.d. ~ 1 970	n.d. ~ 63.3	

注:n.d.表示未检出;BPA 表示双酚 A;BPAF 表示双酚 AF;BPAP 表示双酚 AP;BPB 表示双酚 B;BPF 表示双酚 F;BPP 表示双酚 P;BPS 表示双酚 S;BPZ 表示双酚 Z。

Note: n.d. means not detected; BPA means bisphenol A; BPAF means bisphenol AF; BPAP means bisphenol AP; BPB means bisphenol B; BPF means bisphenol F; BPP means bisphenol P; BPS means bisphenol S; BPZ means bisphenol Z.

表2　双酚类化合物在食品中的平均浓度和检出率

Table 2　Mean concentrations and detection frequencies of bisphenols in food

样本 Sample	国家 Country	平均浓度/(ng·g^{-1})(检出率/%) Mean concentrations/(ng·g^{-1}) (Detection frequencies/%) BPA	BPAF	BPAP	BPB	BPF	BPP	BPS	BPZ	ΣBPs	参考文献 References
饮料 Beverages		0.235 (6.45)	n.d. (0)	n.d. (0)	n.d. (0)	n.d. (0)	0.025 (3.23)	0.007 (3.23)	n.d. (0)	0.341 (25.8)	[25]
乳制品 Dairy products		2.55 (48.28)	0.028(10.3)	0.185 (31)	0.014 (3.45)	0.134 (17.2)	n.d. (0)	0.04 (13.8)	n.d. (0)	2.99 (75.9)	
油 Fats and oils		1.90 (80)	0.006 (20)	n.d. (0)	n.d. (0)	0.255 (60)	n.d. (0)	n.d. (0)	n.d. (0)	2.23 (100)	
鱼/海鲜 Fish/seafood		3.23 (73.9)	0.01 (4.35)	0.007(21.7)	n.d. (0)	4.63 (17.4)	n.d. (0)	0.021 (26.1)	n.d. (0)	7.95 (91.3)	
谷类/谷制品 Cereals/cereal products	美国	0.605 (56.3)	0.005 (2.08)	0.013 (8.33)	0.017 (12.5)	0.079(2.08)	0.013 (4.17)	0.013 (14.6)	n.d. (0)	0.887 (70.8)	
肉/肉制品 Meat/meat products	United States	0.852 (76.5)	0.014 (7.84)	0.049 (11.8)	n.d. (0)	1.34 (7.84)	0.353 (3.92)	0.609 (43.1)	0.026 (1.96)	3.25 (88.2)	
水果 Fruits		0.532 (45)	0.021 (30)	0.061 (10)	n.d. (0)	0.025 (3.23)	n.d. (0)	0.009 (25)	n.d. (0)	0.698 (75)	
蔬菜 Vegetables		8.99 (66.7)	0.009 (15.6)	0.124 (6.67)	n.d. (0)	1 (17.8)	0.473 (4.44)	0.018 (22.2)	0.076 (11.1)	10.7 (80)	
其他 Others		9.97 (53.3)	0.012 (62)	0.013 (6.67)	n.d. (0)	1.21 (13.3)	0.562 (13.3)	0.005 (6.67)	n.d. (0)	11.8 (86.7)	
所有 All		3 (56.9)	0.012 (10.5)	0.059 (11.2)	0.013 (2.62)	0.929 (10.1)	0.207 (3.37)	0.13 (20.9)	0.034 (2.25)	4.38 (74.5)	
谷类/谷制品 Cereals/cereal products		5.6 (69.2)	0.005 (2.6)	0.027 (5.1)	0.014 (5.1)	0.131 (12.8)	0.133 (5.1)	0.042 (23.1)	n.d. (0)	5.97 (76.9)	[26]
肉/肉制品 Meat/meat products		0.579 (55)	0.012 (10)	0.102 (10)	0.52 (5)	0.429 (25)	0.53 (15)	2.16 (30)	0.066 (10)	4.39 (85)	
鱼/海鲜 Fish/seafood		14.1 (100)	0.088 (36.4)	0.006 (9.1)	n.d. (0)	1.74 (45.5)	n.d. (0)	0.564 (72.7)	n.d. (0)	16.5 (100)	
蛋 Eggs		2.15 (63.9)	0.02 (36.4)	0.01 (18.2)	0.014 (9.1)	0.123 (27.3)	0.335 (9.1)	n.d. (0)	n.d. (0)	2.69 (90.9)	
牛奶/奶制品 Milk/milk products		1.47 (82.4)	n.d. (0)	0.063 (11.8)	n.d. (0)	0.384 (52.9)	0.037 (5.9)	0.012 (11.8)	n.d. (0)	2.01 (94.1)	
豆制品 Bean products		6.48 (63)	0.006 (7.4)	0.029 (7.4)	0.013 (3.7)	0.05 (3.7)	0.317 (11.1)	0.054 (14.8)	0.077 (3.7)	7.03 (70.4)	
水果 Fruits	中国	7.76 (85)	0.008 (25)	0.007 (10)	n.d. (0)	0.1 (10)	n.d. (0)	0.011 (15)	0.252 (15)	8.16 (100)	
蔬菜 Vegetables	China	2.88 (59.5)	0.031 (21.4)	4.68 (56.9)	n.d. (0)	15.4 (26.2)	3.27 (16.7)	0.644 (31)	0.037 (4.8)	27 (90.5)	
零食 Snacks		4.16 (73.1)	0.005 (3.8)	n.d. (0)	n.d. (0)	0.14 (7.7)	0.091 (3.8)	0.065 (34.6)	n.d. (0)	4.51 (80.8)	
饮料 Beverages		15.5 (75)	n.d. (0)	n.d. (0)	n.d. (0)	n.d. (0)	n.d. (0)	n.d. (0)	n.d. (0)	15.6 (75)	
烹饪油 Cooking oils		1.92 (54.5)	0.017 (9.1)	n.d. (0)	0.047 (9.1)	0.194 (45.5)	n.d. (0)	0.014 (9.1)	n.d. (0)	2.24 (72.6)	
调味品 Condiments		7.19 (25)	0.019 (14.6)	0.065 (6.3)	0.669 (2.1)	0.45 (10.4)	0.595 (2.1)	0.02 (16.7)	0.026 (2.1)	9.03 (45.8)	
其他 Others		0.445 (53.8)	0.009 (15.4)	n.d. (0)	n.d. (0)	0.372 (23.1)	0.067 (7.7)	0.009 (15.4)	n.d. (0)	0.944 (69.2)	
所有 All		4.49 (60.9)	0.016 (13.1)	0.711 (8.3)	0.158 (2.4)	2.5 (19.4)	0.686 (6.9)	0.287 (22.5)	0.05 (3.1)	9.35 (77.5)	
番茄罐头 Canned tomatoes	意大利 Italy	19.62 (52.4)			8.85 (21.4)						[27]
芥末酱 Mustard consumption	瑞典 Sweden				1.85						[28]

注:n.d.表示未检出;BPA 表示双酚 A;BPAF 表示双酚 AF;BPAP 表示双酚 AP;BPB 表示双酚 B;BPF 表示双酚 F;BPP 表示双酚 P;BPS 表示双酚 S;BPZ 表示双酚 Z;ΣBPs 表示总双酚类化合物。

Note: n.d. means not detected; BPA means bisphenol A; BPAF means bisphenol AF; BPAP means bisphenol AP; BPB means bisphenol B; BPF means bisphenol F; BPP means bisphenol P; BPS means bisphenol S; BPZ means bisphenol Z; ΣBPs means sum of bisphenols.

表 3 双酚类化合物在人体中的暴露水平(中位数)和检出率

Table 3 Exposure levels (median) and detection frequencies of bisphenols in human

样本 Sample	国家 Country	年份 Year	人群 Population	单位 Unit	浓度中位数/($ng \cdot g^{-1}$) (检出率/%) Median of concentrations/($ng \cdot g^{-1}$) (Detection frequencies/%)							参考文献 References
					BPA	BPAF	BPAP	BPF	BPP	BPS	BPZ	
尿液 Urine	韩国 South Korea	2011—2012	孕妇 Pregnant women	$\mu g \cdot L^{-1}$	4.55 (90.18)						[29]	
血清 Serum				$\mu g \cdot L^{-1}$	1.56 (100)							
胎盘 Placenta				$\mu g \cdot kg^{-1}$	0.53 (82.10)							
母乳 Breast milk				$\mu g \cdot L^{-1}$	0.74 (79.53)							
血清 Serum			新生儿 Newborns	$\mu g \cdot L^{-1}$	1.71 (99.57)							
尿液 Urine				$\mu g \cdot L^{-1}$	4.75 (82.24)							
血清 Serum	中国 China	2017	孕妇 Pregnant women	$ng \cdot mL^{-1}$	0.6 (76)	n.d. (25)	n.d. (13)		n.d. (8)	n.d. (30)		[30]
尿液 Urine				$ng \cdot mL^{-1}$	0.9 (100)	0.2 (100)	n.d. (47)		n.d. (7)	0.6 (100)		
血清 Serum			新生儿 Newborns	$ng \cdot mL^{-1}$	1.5 (88)	n.d. (24)	n.d. (22)		n.d. (19)	0.028 (63)		
羊水 Amniotic fluid				$ng \cdot mL^{-1}$	0.2 (67)	0.02 (80)	n.d. (27)		n.d. (13)	0.02 (67)		
尿液 Urine	德国 Germany	2015—2017	儿童 Children	$\mu g \cdot L^{-1}$	1.82 (96)							[31]
尿液 Urine	中国 China	2017—2018	儿童 Children	$ng \cdot L^{-1}$	369 (97.5)	n.d. (46.2)		n.d. (21.2)		18.8 (98.8)		[32]
尿液 Urine	中国 China	2017	成年人 Adults	$\mu g \cdot L^{-1}$	1.74 (99.4)	0.002(58.1)	n.d. (8.8)	0.08 (74.6)	n.d. (0)	n.d. (25.9)	n.d. (15)	[34]
尿液 Urine	日本 Japan	2012—2017	儿童 Children	$ng \cdot mL^{-1}$	0.89 (89)	n.d. (19)	n.d. (23)	0.07 (83)		0.11 (78)	n.d. (14)	[33]
尿液 Urine	挪威 Norway	2017—2018	儿童 Children	$ng \cdot mL^{-1}$	1.05 (86)	n.d. (12)		0.14 (97)		0.12 (83)	n.d. (37)	[35]
下丘脑 Hypothalamic	荷兰 Netherlands		成年人 Adults	$ng \cdot g^{-1}$	0.68 (96)							[36]
白质 White-matter					0.82 (90)							
头发 Hair	希腊 Greece		孕妇 Pregnant women	$pg \cdot mg^{-1}$	n.d. (37)					n.d. (34)		[37]
脂肪组织 Adipose tissue	西班牙 Spain	2015	成年人 Adults	$ng \cdot g^{-1}$	n.d. (42.9)							[38]

注:n.d.表示未检出;BPA 表示双酚 A;BPAF 表示双酚 AF;BPAP 表示双酚 AP;BPB 表示双酚 B;BPF 表示双酚 F;BPP 表示双酚 P;BPS 表示双酚 S;BPZ 表示双酚 Z。

Note: n.d. means not detected; BPA means bisphenol A; BPAF means bisphenol AF; BPAP means bisphenol AP; BPB means bisphenol B; BPF means bisphenol F; BPP means bisphenol P; BPS means bisphenol S; BPZ means bisphenol Z.

2.2　神经毒性

神经元的发育过程(包括增殖、迁移、分化、突触发生、髓鞘形成和凋亡)从胚胎期一直延续到青春期[50]。大量研究表明,双酚类化合物暴露可引起中枢神经系统发育和功能异常,包括神经可塑性改变、神经发育不良、神经细胞凋亡和认知功能障碍[51-52]。比如,长期暴露于 BPA (0.1、0.5、1、5 和 10 μmol·L^{-1}),人谷氨酸神经元的神经突触生长呈浓度依赖性减少,高浓度 BPA (1 μmol·L^{-1}和 10 μmol·L^{-1})使树突的总长度和分枝数减少,顶端树突的分枝数减少[52]。细胞内 Ca^{2+}信号对突触可塑性起重要作用,BPA 对海马神经元中谷氨酸诱导 $c(Ca^{2+})$升高有影响:1 ~10 pmol·L^{-1}时 BPA 抑制谷氨酸诱导 $c(Ca^{2+})$升高,1 ~100 nmol·L^{-1}时会增强谷氨酸诱导 $c(Ca^{2+})$升高[53]。青春期小鼠暴露于 BPA,降低成年期雄性小鼠社交能力,抑制其与异性社会交往,这可能是因为 BPA 具有弱雌激素效应[54]。青春期雄性小鼠暴露于 BPA,其成年期脑内睾酮水平和外侧隔、杏仁核、终纹床核的雄激素受体(AR)水平,以及杏仁核和终纹床核的雌激素受体 α 和 β (ERα/β)水平下调,扰乱雌性激素和雄性激素对精氨酸加压素(arginine vasopressin, AVP)系统的调节,损害雄性小鼠的社会认知能力[55]。BPA 和 BPS 短期暴露会导致斑马鱼(*Danio rerio*)受精后 24 h 胚胎神经数量显著增加,并进一步诱导幼虫行为亢进[56]。斑马鱼暴露于 BPF,幼鱼的星形胶质细胞或小胶质细胞被激活,在 0.5 μg·L^{-1} BPF 暴露水平下中枢神经细胞凋亡,不同浓度的 BPF 均可显著影响斑马鱼受精 72 h 时运动神经元的发育,并抑制轴突生长[5]。用极低剂量的 BPA 和 BPS 处理斑马鱼胚胎,下丘脑内神经元的发生分别增加了 180% 和 240%,与运动过度活跃有关[56]。

甲状腺激素在妊娠期和儿童期的神经元迁移、突触发生和髓鞘形成中起关键作用[57]。妊娠期小鼠口服 BPA 母鼠和胎鼠血清中甲状腺素和三碘甲状腺原氨酸水平均低于对照组,促甲状腺素水平高于对照组[58]。

一些流行病学研究也发现双酚类化合物对儿童认知、行为等有影响。148 名新生儿脐带血中 BPA 浓度与其 7 岁时的智商分数、言语理解能力指数以及知觉推理指数呈负相关[59]。Braun 等[60]发现 BPA 浓度增加 1 倍,男孩的工作记忆能力得分会下降 1 分,而女孩的工作记忆能力会提高 0.5 分。自闭症谱系障碍儿童体内 BPA 的浓度是正常儿童的 3 倍[61]。

2.3　呼吸和免疫毒性

环境污染物破坏发育中的呼吸和免疫系统,可能降低抗感染能力和肺功能,增加过敏风险。BPF 和 BPS 增加斑马鱼早期发育阶段活性氧含量、一氧化氮含量、一氧化氮合酶活性、细胞因子和趋化因子以及免疫相关基因的表达,此外 BPS 和 BPF 均可诱导雌激素受体和核转录因子(nf-*κ*b)的表达,而雌激素受体和 nf-*κ*b 拮抗剂可阻断免疫相关基因的表达,表明 BPS 和 BPF 对鱼类免疫应答功能有影响[3]。BPA (0.1 μg·L^{-1})显著干扰鲤鱼(*Cyprinus carpio*)幼鱼免疫应答[62],增加斑马鱼幼鱼先天免疫相关基因表达[63]。产前暴露于 BPA 使雄性大鼠的相对胸腺质量降低[64]。

流行病学研究表明,产前暴露于 BPA 对儿童的气喘和哮喘有影响(表 4)。妊娠期母亲尿液中 BPA 的浓度与儿童发生气喘的风险正相关(相对风险度(relative ratio, RR)为 1.20)[65]。各个妊娠期母亲尿液中 BPA 的浓度水平与儿童期哮喘发生风险呈正相关,且在 Buckley 等[66]的研究中,这种关联仅在男孩中发现(比值比(odds ratio, OR)为 3.04)。产后暴露于 BPA 表现出类似的影响。例如,Kim 等[67]发现韩国 7 ~8 岁儿童 BPA 尿液浓度与气喘(OR 为 2.48)和哮喘(风险比(hazard ratio, HR)为 2.13)发生呈正相关;哥伦比亚 568 名儿童尿液 BPA 与 7 岁时的气喘发生相关(OR 为 1.4)[68]。

2.4　致肥胖效应

生命早期暴露于 EEDs 可扰乱涉及生长、能量代谢、食欲、脂肪生成和糖-胰岛素稳态的神经内分泌系统,从而促进儿童肥胖[39,69-70]。Héliès-Toussaint 等[71]报道了 BPA 或 BPS 处理小鼠 3T3-L1 脂肪细胞后,脂肪分解减少,而 BPS 处理增加了葡萄糖摄取和瘦素生成。这些结果表明 BPA 和 BPS 通过不同代谢途径参与肥胖和脂肪变性。

围产期暴露于 BPS 使小鼠的雄性后代体质量、肝脏和附睾白色脂肪组织质量、肝脏甘油三酯和胆固醇含量升高[72]。一项元分析研究表明,生命早期暴露于 BPA 与啮齿动物的肥胖体质量、甘油三酯和游离脂肪酸呈显著正相关[73]。

由表 5 可知,产前和产后暴露于酚类化合物对儿童和青少年超重或肥胖有影响。中国上海 1 326 名儿童尿液中高浓度 BPA 与女学生超重有相关性,特别是 9 ~12 岁女孩(OR =2.32)[74]。2 664 名 7 ~11 岁美国儿童尿液中高浓度的 BPA 与肥胖的风险正

相关(OR=2.55),性别分层后,在男孩中这种效应更明显[75]。一项横断面研究发现,女性和 8～11 岁儿童尿液中 BPA 的浓度与 BMI 值的增加显著相关[76]。在 297 名美国儿童的研究中,产前 BPA 浓度与儿童 BMI 无相关性[77]。在一项关于希腊儿童的研究中,产前 BPA 浓度与女孩 BMI 和肥胖指标呈负相关,而在男孩中呈正相关[78]。目前只有 2 项研究探究了 BPA 替代物对儿童和青少年肥胖或超重的影响,这 2 项研究中,BPF 与儿童一般肥胖和腹部肥胖呈正相关[79-80]。

2.5　发育毒性

双酚类化合物可以影响新生儿出生结局,包括出生体质量和胎龄。双酚类化合物具有雌激素效应,与雌激素相关受体-g 结合,影响胎盘功能[81],或者增加孕妇氧化应激反应和不良炎症,影响胚胎着床、胎盘着床和胎儿生长,如宫内生长受限、早产和低出生体质量[82-84]。BPS 可以提高黄体酮水平,而黄体酮对维持妊娠状态和控制分娩起重要作用[85-86]。

动物学实验证明,亚致死浓度的 BPS 和 BPF 抑制斑马鱼幼鱼孵化时间和体长[3]。Qiu 等[87]发现,低剂量 BPA 会缩短斑马鱼孵化时间。Yang 等[88]发现,暴露于 BPF 会降低斑马鱼幼鱼出生体质量和出生长度。在大鼠妊娠第 1～15 天腹腔注射 BPA,胎儿存活率下降,存活胎儿体质量下降[89]。

总结了产前暴露于双酚类化合物对新生儿胎龄和出生体质量影响的流行病学研究(表 6),不同研究得出的结论有诸多不一致之处。在一项关于中国健康婴儿的队列研究中,母亲 BPS 的浓度水平与新生儿胎龄呈正相关[90],一项关于中国武汉的孕妇研究中 BPS 与早产没有关系[91],而在另一项研究中 BPS 与早产呈正相关[92]。在 3 项研究中,母亲尿液中 BPS 的浓度与出生体质量无关[93-95],而在另外 3 项研究中母亲体内 BPS 的浓度与出生体质量升高或降低有关[37,96-97]。BPA 对出生体质量的影响也不一致,呈负相关或无相关性[90,94-95]。在同一篇研究中,不同妊娠时期,双酚类化合物暴露浓度对新生儿出生结局的影响也不同[98]。在美国 PROTECT 队列中,孕妇在妊娠 24～28 周时尿液中 BPS 浓度增加了小于胎龄儿风险,而在妊娠 16～20 周时 BPS 浓度与大于胎龄儿的风险呈正相关[98]。

3　研究展望(Research prospect)

(1) 有必要建立起一套标准化的检测方法

目前,在探究儿童体内暴露水平时,不同研究取样时间、检测方法等都存在一定差异,从而导致在进行暴露水平时空差异对比时存在一定的误差。例如,虽然大多数研究都以儿童第一次晨尿为样本,但未规定具体取样时间以及是否在进食前取样。研究证实,研究对象是否进食、取样时间与进餐时间之差会影响尿液中 BPA 总浓度[102]。此外,不同的前处理方法、化学检测方法导致检出限不尽相同。使用甲基叔丁基醚萃取美国儿童尿液中双酚类化合物,BPF 检出限为 0.074 $ng\cdot mL^{-1}$,检出率为 23.6%[103];而使用固相萃取柱萃取日本儿童尿液中双酚类化合物,BPF 检出限为 0.02 $ng\cdot mL^{-1}$,检出率为 83%[33]。除了研究对象本身的差异,检出限的不同可能也是造成检出率差异的原因之一。因此,有必要建立起一套标准化的检测方法,统一取样细节,规范分析方法,使得在进行不同研究的双酚类化合物检出情况比较时,结果更为客观准确。

(2) 应尽快开展 BPA 替代物对儿童体格发育影响的环境流行病学研究

小鼠动物实验与元分析研究已经明确了生命早期暴露于 BPA 及其主要替代物的致肥胖效应[71-73]。然而,目前对于双酚类化合物对儿童体格发育影响的环境流行病学集中于 BPA[74-78],仅有 2 项研究探究了 BPA 替代物对美国儿童和青少年体格发育的影响[79-80]。儿童肥胖被确定为 21 世纪严重的公共卫生挑战之一。以我国为例,在过去的 40 年里,我国超重和肥胖儿童的数量迅速增加[104]。2005 年,0～6 岁儿童的超重率为 3.4%,肥胖率为 2.0%,7～17 岁儿童和青少年超重率为 4.5%,肥胖率为 2.1%[105]。2015—2019 年,中国 6 岁以下儿童超重率为 6.8%,肥胖率为 3.6%;6～17 岁儿童和青少年超重率为 11.1%,肥胖率为 7.9%[104]。考虑到 BPA 替代物日益广泛的使用、在环境和人体中的生物迁移和生物放大作用,以及儿童超重率、肥胖率的大幅增加,应尽快开展其对儿童体格发育的影响研究。

(3) 有必要开展胎儿脐带血中双酚类化合物实测浓度对新生儿出生结局影响的研究

双酚类化合物可以透过胎盘屏障,直接对胎儿产生影响。但是,由于暴露方式等因素的变化,双酚类化合物的胎盘转运率(即胎儿血浆与母亲血浆浓度的比值)波动较大。例如,Zhang 等[30]发现 BPS、BPA 的胎盘转运率分别为 1.11、1.94;而在绵羊的胎盘灌注模型中,BPS 的胎盘转运率为 0.032[106],BPA 的胎盘转运率为 0.293[107]。因此,以孕妇体内双酚类

表4 产前暴露于 BPA 对儿童气喘和哮喘的影响

Table 4 Effect of prenatal exposure to BPA on wheeze and asthma of children

时期 Stage	年龄 Age	气喘 Wheeze	哮喘 Asthma	参考文献 References
妊娠期 Duration of pregnancy	6个月,14个月,4岁,7岁 6 months, 14 months, 4 years, 7 years	RR 为 1.20 (1.03 ~ 1.40) RR is 1.20 (1.03 ~ 1.40)	RR 为 1.21 (0.94 ~ 1.57) RR is 1.21 (0.94 ~ 1.57)	[65]
妊娠晚期 The third trimester of pregnancy	6 ~ 7岁 6 ~ 7 years	NA	OR 为 1.66 (1.04 ~ 2.66),男孩 OR 为 3.04 (1.38 ~ 6.68),女孩 OR 为 0.94 (0.48 ~ 1.84) OR is 1.66 (1.04 ~ 2.66), OR is 3.04 (1.38 ~ 6.68) of boys, OR is 0.94 (0.48 ~ 1.84) of girls	[66]
妊娠中期 The second trimester of pregnancy	7岁 7 years	NA	OR 为 1.03 (0.68 ~ 1.55) OR is 1.03 (0.68 ~ 1.55)	[99]
妊娠中期 The second trimester of pregnancy	8个月 ~ 5岁 8 months ~ 5 years	无关 No relation	HR 为 1.23 (0.97 ~ 1.55) HR is 1.23 (0.97 ~ 1.55)	[100]

注:NA 表示未进行分析;OR 表示比值比;HR 表示风险比;RR 表示相对风险度;BPA 表示双酚 A。

Note: NA means no analysis; OR means odds ratio; HR means risk ratio; RR means relative risk; BPA means bisphenol A.

表5 产前和产后暴露于双酚类化合物对儿童和青少年肥胖和超重的影响

Table 5 Effect of prenatal and postnatal exposure to bisphenols on childhood obesity and overweight

国家 Country	暴露时间 Exposure time	年龄 Age	结论 Conclusions	参考文献 References
中国 China	产后 Postnatal		尿液中 BPA 水平高与女生超重有关 High urinary level of BPA was associated with overweight risk of girls	[74]
美国 United States	产后 Postnatal	6 ~ 18	与 BPA 最低四分位(1.5 ng·mL^{-1})的儿童相比,最高四分位(5.4 ng·mL^{-1})的儿童肥胖的 OR 为 2.55;观察到的阳性关联主要出现在男孩(OR=3.80) The OR for obesity children in the highest quartile (5.4 ng·mL^{-1}) was 2.55, compared to those in the lowest quartile (1.5 ng·mL^{-1}) of BPA; the observed positive association was mainly in boys (OR=3.80)	[75]
中国 China	产后 Postnatal	8 ~ 15	在调整年龄和性别后,尿液中 BPA 的浓度与 BMI 值的增加显著相关 Urinary level of BPA was positively associated with BMI, after adjusted for age and sex	[76]
美国 United States	产前和产后 Prenatal and postnatal	2 ~ 5	母亲尿液中 BPA 浓度每增加 10 倍,2 ~ 5 岁超重的儿率就会适度降低(OR=0.65, P>0.5) For every 10-fold increase in maternal urinary concentration of BPA, the odds of overweight at 2 to 5 years were slightly reduced (OR=0.65, P>0.5)	[77]

续表5

国家 Country	暴露时间 Exposure time	年龄 Age	结论 Conclusions	参考文献 References
希腊 Greece	产前 Prenatal	4	4 岁儿童尿液中 BPA 每增加 10 倍,BMI Z 评分(β=0.2),腰围(β=1.2)和皮肤褶皱厚度之和(β=3.7)就升高;在女孩中,产前 BPA 与 BMI 和肥胖指标呈负相关,而在男孩中呈正相关 For every 10-fold increase in urinary BPA of 4-year-old children, the BMI Z score (β=0.2), waist circumference (β=1.2) and sum of skin fold thickness (β=3.7) would increase; for girls, prenatal BPA was negatively associated with BMI and obesity indicators, while it was positively associated for boys	[78]
美国 United States	产后 Postnatal	6～19	尿 BPS 的对数转化浓度与一般肥胖患病率的增加相关(OR=1.16)和腹部肥胖(OR=1.13);BPF 检测(与未检测)与腹部肥胖患病率(OR=1.29)和 BMI Z 得分增加(β=0.10)相关;BPA 和总双酚与一般肥胖、腹部肥胖或任何体质量结果均无统计学显著相关 Urinary log-transformed concentrations of BPS were associated with increased risk of general obesity (OR=1.16) and abdominal obesity (OR=1.13); BPF detected (vs. no detected) was associated with increased prevalence of abdominal obesity (OR=1.29) and BMI Z score (β=0.10); neither BPA nor total bisphenols were associated with general obesity, abdominal obesity or any weight outcome	[79]
美国 United States	产后 Postnatal	6～17	BPA 和 BPF 与一般和腹部肥胖的关系是正相关,BPS 与肥胖无关,BPA 的 OR 值为 1.54,BPF 的 OR 值为 1.36;此外,BPA 和 BPF 在男孩身上的相关性比女孩强 BPA and BPF were positively associated with general and abdominal obesity, with OR of 1.54 for BPA and 1.36 for BPF, while BPS was not associated with obesity; in addition, BPA and BPF were more strongly correlated for boys	[80]

注:BPA 表示双酚 A;BPF 表示双酚 F;BPS 表示双酚 S。

Note: BPA means bisphenol A; BPF means bisphenol F; BPS means bisphenol S.

表 6　双酚类化合物对新生儿胎龄和出生体质量的影响

Table 6　Effect of bisphenols on gestational age and birth weight of newborns

样本 Sample	样本来源 Source of sample	国家 Country	年份 Year	时期 Stage	结论 Conclusions	参考文献 References
头发 Hair	母亲 Maternal	希腊 Greece	2018	孕中期 The second trimester of pregnancy	BPA 与出生体质量和早产无关,BPS 与出生体质量升高有关 BPA was not associated with birth weight and preterm birth, while BPS was positively associated with birth weight	[37]
尿液 Urine	母亲 Maternal	中国 China	2012—2014	妊娠 32～42 周 At 32～42 weeks gestation	BPS 与胎龄呈正相关,BPA 与胎龄减少有关,二者与出生体质量无关 BPS was positively associated with gestational age, and BPA was associated with reduced gestational age; BPA and BPS were not associated with birth weight	[90]

续表6

样本 Sample	样本来源 Source of sample	国家 Country	年份 Year	时期 Stage	结论 Conclusions	参考文献 References
尿液 Urine	母亲 Maternal	中国 China	2014—2015	孕早、中和晚期 Three trimesters of pregnancy	母体孕期平均 BPA 浓度与妊娠期缩短和早产风险增加显著相关 During pregnancy, maternal mean concentration of BPA was significantly associated with shorter gestational age and increased risk of preterm delivery	[91]
尿液 Urine	母亲 Maternal	美国 United States	2006—2008	孕早期 The first trimester of pregnancy	BPS 与早产正相关 BPS was positively associated with preterm birth	[92]
尿液 Urine	母亲 Maternal	美国 United States	2006—2008	孕早、中和晚期 Three trimesters of pregnancy	BPS 与出生体质量不相关 BPS was no associated with birth weight	[93]
尿液 Urine	母亲 Maternal	美国 United States	2015	孕早、中和晚期 Three trimesters of pregnancy	BPA 与出生体质量下降有关，BPS 与出生体质量不相关 BPA was negatively associated with birth weight, while no association between BPS and birth weight	[94]
血浆 Plasma	母亲 Maternal	中国 China	2015—2018		BPA 和 BPF 与出生体质量负相关，BPS 与出生体质量无关 BPA and BPF were negatively associated with birth weight, while no association between BPS and birth weight	[95]
尿液 Urine	母亲 Maternal	中国 China	2013—2015	孕早、中和晚期 Three trimesters of pregnancy	在某些妊娠期间，尿中 BPF 和 BPS 浓度与出生体质量、出生长度或体质量指数显著降低相关 During pregnant stages, urinary concentrations of BPF and BPS were negatively associated with birth weight, birth body length or body mass index	[96]
尿液 Urine	母亲 Maternal	美国 United States	2012—2015	孕早期 The first trimester of pregnancy	BPS 与较低出生体质量有关 BPS was associated with lower birth weight	[97]
尿液 Urine	母亲 Maternal	美国 United States	2011—2017	妊娠 16～20, 20～24, 24～28 周 At 16～20, 20～24, 24～28 weeks gestation	妊娠 24～28 周时，BPS 与小于胎龄儿几率的增加有关，妊娠 16～20 周时与大于胎龄儿几率的增加有关 BPS was associated with an increased risk of a small gestational age baby at 24～28 weeks gestation, and an increased risk of a larger gestational age baby at 16～20 weeks gestation	[98]
血浆 Plasma	脐带血 Cord blood	中国 China	2017—2018		BPAF 与早产和出生体质量显著正相关 BPAF was positively associated with preterm delivery and birth weight	[101]

注：BPA 表示双酚 A；BPF 表示双酚 F；BPS 表示双酚 S。

Note: BPA means bisphenol A; BPF means bisphenol F; BPS means bisphenol S.

化合物的浓度代表胎儿的产前暴露水平,可能会低估或高估双酚类化合物对新生儿出生结局的影响,这可能是造成目前不同研究结论不一致的原因之一(表 6)。因此,有必要开展胎儿脐带血中双酚类化合物实测浓度对新生儿出生结局影响的研究。

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