环 境 化 学
ENVIRONMENTAL CHEMISTRY
第 41 卷第 1 期 2022 年 1 月
Vol. 41, No. 1 January 2022

DOI:10.7524/j.issn.0254-6108.2020090801
顾俊婕, 胡 曼, 耿 阳, 等. 有机磷酸酯阻燃剂的人群暴露和甲状腺毒性的研究进展[J]. 环境化学, 2022, 41(1): 31-45.
GU Junjie, HU Man, GENG Yang, et al. A review of organophosphate esters (OPEs): Human exposure and toxicities in thyroid[J]. Environmental Chemistry, 2022, 41 (1): 31-45.

有机磷酸酯阻燃剂的人群暴露和甲状腺毒性的研究进展*

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摘 要 有机磷酸酯（organophosphate esters，OPEs）是使用最为广泛的有机磷阻燃剂，并兼具增塑剂、消泡剂和萃取剂等功能，被广泛用于电子产品、建筑材料和塑料材料等中，导致其在环境介质中普遍存在，对生态系统和人体健康构成巨大威胁. 作为一种新型环境污染物，OPEs 的人群暴露特征和生物毒性成为环境健康领域的研究热点. 本文系统综述了 OPEs 的人群暴露特征和甲状腺毒性的研究进展，最后对存在的问题和未来研究方向进行了分析和展望.

关键词 有机磷酸酯，人群暴露，甲状腺毒性，有机磷阻燃剂.

A review of organophosphate esters (OPEs): Human exposure and toxicities in thyroid

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Abstract Organophosphate esters (OPEs) are the most widely used organophosphorus flame retardant and has the functions of plasticizer, defoamer and extractant, added in electronic products, building materials and plastic materials, etc. The widespread use of OPEs has resulted in their ubiquitous occurrence in environmental media, which pose a threat to both ecosystems and human health. As a type of emerging environmental pollutants, human exposure to OPEs and related toxicity have become a research hotpot in the field of environmental health. In this paper, the research progresses on the population exposure to several kinds of OPEs and its toxicities in thyroid system were summarized. Finally, the gaps in our knowledge of human exposure assessment and thyroid toxicity of OPEs were highlighted and critical directions for future studies were proposed.

Keywords organophosphate esters，human exposure，thyroid toxicity，organophosphate flame retardants.

2020 年 9 月 8 日收稿(Received：September 8，2020).

＊ 国家重点研发计划 (2017YFC1600500) 和国家自然科学基金 (81373089) 资助.

Supported by the scientific National Key R&D Program of China (2017YFC1600500) and the National Natura Science Foundation of China (81373089).

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有机磷酸酯(organophosphate esters, OPEs)阻燃剂是使用最为广泛的有机磷阻燃剂[1]，兼有增塑功能和润滑效果[2]，广泛应用于工程塑料、聚氨酯泡沫塑料、树脂以及电子设备、家装饰品、纺织品和涂料等产品[3－4]. 随着溴系阻燃剂(brominated flame retardants, BFR)主要是多溴二苯醚(polybrominated diphenyl ethers, PBDEs)从 2004 年开始逐步在全球限制使用，OPEs 阻燃剂作为其优秀替代品，在产量和用量上正快速增长[5－6]. 2005 年欧盟 OPEs 的用量达 8.5 万吨，2011 年用量为 50 万吨，2015 年约为 68 万吨[7]；而中国 OPEs 的消费量在 2011 年达到 10 万吨，并以每年 15% 的速率增长[5].

OPEs 阻燃剂是磷酸上的 H 被 3 个取代基团取代的产物. 根据取代基的不同，OPEs 可分为 3 类：氯代、烷烃类和芳基类 OPEs. 不同理化性质影响 OPEs 的环境行为和生物毒性[8]. OPEs 属于添加型阻燃剂，对材料的物理机械性能影响较小[9]，兼有增塑功能和润滑效果[2]，广泛应用于工程塑料、聚氨酯泡沫塑料、树脂以及电子设备、家装饰品、纺织品和涂料等产品[3－4]. OPEs 主要以物理添加方式进入到材料中，在产品的生产、使用、处理和回收的过程中，容易通过挥发、溢出或磨损等方式释放到环境介质中[3]，具有一定的环境持留性. OPEs 已在大气[10－16]、灰尘[16－20]、水体[21－24]、沉积物[25－26]、土壤[26－27] 和食物[26, 28] 等环境介质中被检出. 毒理学研究表明，OPEs 具有免疫毒性、内分泌干扰效应、生殖毒性和神经毒性并具有致癌作用[6, 29－31].

作为一类新兴环境污染物，OPEs 可通过皮肤接触、灰尘摄入、呼吸和饮食等途经进入人体，对人类健康造成潜在危害[32]. OPEs 在人群中暴露情况及其可能引起的各种不良健康效应受到广泛关注[33]. 当前研究主要集中于孕妇人群 OPEs 暴露对后代生长发育的影响[34－36]. 也有研究报道，OPEs 暴露与人群甲状腺肿瘤发生有关联[37]. 甲状腺激素和甲状腺激素受体分布于全身脏器和细胞，对于调控个体生长发育和维持机体新陈代谢起着重要作用. 考虑到 OPEs 具有内分泌干扰效应，OPEs 暴露的甲状腺毒性研究日益受到学术界关注. 鉴于当前有关 OPEs 的研究报道集中于环境赋存、环境行为和生态毒理学[38－39]，而对于 OPEs 的人群暴露及甲状腺毒性的综述报道较少，本文基于国内外最新研究进展，对常见 OPEs 阻燃剂的人群暴露及其甲状腺毒性分别进行综述.

1 OPEs 的人群暴露 (Population exposure to OPEs)

1.1 外暴露来源与暴露途经

人体可通过呼吸道吸入、经口摄入和皮肤吸收等途经暴露于 OPEs[24, 40－41]. 据估算，人类大概有 70%—90% 的时间是在室内中度过，材料和商品中 OPEs 的释放首先影响室内环境进而扩散到室外，室内环境中 OPEs 的浓度水平是室外环境的几百倍，室内空气和灰尘的污染可通过吸入、手口接触和皮肤吸收等多种途径影响到人们. 故空气、灰尘吸入以及皮肤暴露于灰尘被认为是室内环境 OPEs 首要暴露途径[42]. 具有挥发性的磷酸三苯酯 (triphenyl phosphate, TPHP)、磷酸三丁酯 (tri-n-butyl phosphate, TnBP)、磷酸三(丁氧基乙基)酯 (tributoxyethyl phosphate , TBOEP)、磷酸三(2-氯乙基)酯 (tri(2-chloroethyl) phosphate, TCEP)、磷酸三乙酯 (triethyl phosphate, TEP) 和磷酸三 (2-氯异丙基) 酯 (tris(1-chloro-2-propyl) phosphate, TCIPP) 易以蒸气形式存在大气或者吸附在大气颗粒物上，是室内空气和灰尘中常见 OPEs 类型. 其中，TCEP 具有较高化学稳定性，是道路灰尘的主要检出物，比起主要通过灰尘摄入的 TBOEP 和 TPHP，空气吸入是主要途径[43]. 氯代 OPEs 具有高持久性，对降解具有相对稳定性，可在一段时间内在室内环境中聚集，其中 TCIPP 检出率最高，其吸入暴露远远超过消化道吸收途径[43]. 与灰尘有关的 OPEs 对人类来说具有相当大的威胁，因为它们可以通过空气吸入、摄入重新悬浮的灰尘颗粒、皮肤吸收和手口接触而误食等多种方式联合暴露.

经膳食和饮水摄入是人体 OPEs 暴露另一个重要途径[45]. 食物中 OPEs 有两种来源方式[46－47]. 一是环境介质中 OPEs 通过食物链进入食物. Zhang 等在中国北部湾某海鲜养殖场的池水、沉积物、饲料和养殖物均检测出 11 种 OPEs，且发现 OPEs 在沉积物、饲料和养殖物中平均浓度呈递增趋势，提示 OPEs 可在食物链中迁移并在生物体内富集[48]. Wang 等在肉类、海鲜、乳制品、谷物、食用油和食品包装上均检出 15 种 OPEs，其中肉类 ΣOPEs(Median：6.76 $\mathrm{ng \cdot g^{-1} ww}$)和海鲜(Median：7.11 $\mathrm{ng \cdot g^{-1} ww}$)的检出浓度最高；肉类占成人 OPEs 膳食摄入总量的 47%，而乳制品占儿童 OPEs 膳食摄入总量的 52%[49].

Ding 等分析中国东部某城市的鸡肉、猪肉、鱼类、蔬菜、豆制品、谷物和蛋类等食品样品[50], 其中 10 种 OPEs 的总残留浓度为 1.1—9.6 ng·g^{-1} fw(鲜重), 谷物是城乡居民膳食 OPEs 的主要来源(占总膳食的 55.5%—62.5%)且残留水平高(4.9 ng·g^{-1} fw). 二是食物在生产、加工和储存过程被包装材料中 OPEs 污染. 尽管不同国家人群经食物摄入 OPEs 类型存在较大差异, 但是作为食品包装材料成分的 EHDPP, 在世界各国的加工食品中被普遍检出. 对于婴幼儿来说, 母乳是一个重要的食物暴露源, 在多个亚洲和欧洲国家哺乳期的妇女母乳中均有检出芳基类和烷基类 OPEs[51–52].

皮肤直接接触含 OPEs 的水或者产品也是人体暴露 OPEs 途经之一. 皮肤吸收一般通过监测经擦拭皮肤的湿巾纸中 OPEs 含量来评估分析, TCEP、TCIPP 和磷酸三(1,3-二氯异丙基)酯 (Tris(1,3-dichloroisopropyl) phosphate, TDCIPP) 被证实可经皮肤吸收暴露[53–54], 而且疏水性较强的化合物皮肤吸收可能会时间滞后[55]. TDCIPP、TCEP 和 TPHP 在擦拭皮肤的湿巾中检出率超 90.6%, 被发现可能存在手口接触摄入和皮肤吸收途径暴露[56–57]. 一些研究发现, 从 51 名加拿大妇女的手、手机和家庭粉尘中检出 OPEs 能够解释其尿液 OPEs 总浓度 8%—33% 的变异[58], 3 名美国成年人手中 TDCIPP 和 TPHP 浓度与尿样代谢产物具有统计学关联[56], 而 26 名美国妇女通过指甲油暴露于 TPHP, 这说明成年人可通过手口接触和皮肤接触暴露于 OPEs.

1.2　内暴露监测

生物监测是 OPEs 人群内暴露监测主要实施手段. 尿液是最常用的评估人体 OPEs 内暴露的生物材料. 体内和体外实验证实, OPEs 在体内容易通过 I 相和 II 相代谢反应形成有机磷酸二酯 (di-OPEs) 从尿液排出[59], 故国内外许多研究将人体尿液中 di-OPEs 作为暴露标志物, 用来评估人体 OPEs 内暴露[29, 60](见表 1). 除了尿液, 血液和羊水也被用于监测 di-OPEs 的生物材料. Hou 等分析尿液和匹配的血液后发现, 除了 BCIPP 和 di-*o*-cresyl phosphate(DoCP), 其余 di-OPEs(如 DnBP、DiBP、BBOEP、BCEP、BDCIPP、DPHP 和 BEHP 等)在尿液中检出频率和浓度均高于血液样本, 而相对于全血, 血清样本中所有 9 种目标 di-OPEs 的检出频率和浓度均较低[61]. Bai 等在我国汕头某电子垃圾地区的孕妇尿液及配对的羊水中均检出 DnBP (GM: 2.9 ng·mL^{-1}, 1.3 ng·mL^{-1}) 和 DPHP (GM: 0.94 ng·mL^{-1}, 0.12 ng·mL^{-1}), 且尿液样本浓度比羊水样本高 2 倍以上[62]. 另一方面, 有机磷酸三酯 (tri-OPEs) 也被作为暴露标志物, 用于评估人体 OPEs 内暴露. 血样样本应用最多, 其次是母乳(见表 2). 头发中 OPEs 被认为是来自空气和灰尘的外暴露和内暴露的组合. Kucharska 等分析 48 个母亲和 54 个子女的头发和尿液样本, 发现头发可作为 OPEs 暴露评估的指示材料[63]. Ding 等分析我国华东地区 50 份人体胎盘样本, 检出率最高的是 TCEP, 其次是 TBOEP 和 TPHP, tri-OPEs 检出量(34.4—862 ng·g^{-1} lw)比多溴二苯醚(PBDEs)检出浓度高一个数量级, 这是第一次研究胎盘中 OPEs 暴露[64].

表 1　主要 di-OPEs 的国内外人群平均内暴露水平(pg·mL^{-1})

Table 1　Typical di- OPEs levels among population reported in various studies worldwide(pg·mL^{-1})

国家或地区 Sample site	年份 Time	人群 Population	年龄/岁 Year	数量^a *n*	样本类型 Type	芳基类 Aryl-	烷基类 Alkyl-				含氯类 Chlorinated-			参考文献 Reference
						DPHP	DEP	DnBP	BEHP	BBOEP	BCEP	BCIPP	BDCIPP	
中国	2018*	电子拆解工人	—	88	尿液	700	—	—	—	—	1770	N.D.	230	Yan等[70]
		垃圾回收厂工人	—	30	尿液	110	—	—	—	—	1440	N.D.	220	
	2018*	成人	17—87	52	尿液	177	—	230	6760	2650	2570	150	291	Hou等[61]
				57	全血	92	—	123	4480	328	<LOQ	370	<LOQ	
				57	血清	14	—	<LOQ	3080	<LOQ	<LOQ	121	<LOQ	
	2016—2017*	成人	—	26	尿液	240	—	48	—	110	—	—	230	Tao等[71]
	2016—2017	孕妇	—	15	尿液	940 1200*	—	2900 2200*	—	87	—	—	270	Bai等[62]
					羊水	120 180*	—	1300 1200*	—	<LOQ	—	—	<LOQ	
	2016—2017	成人和儿童	4—90	180	尿液	32.4	376	8.04	49.1	69.1	1.73	22.8	5.31	Sun等[61]

续表 1

国家或地区 Sample site	年份 Time	人群 Population	年龄/岁 Year	数量[a] *n*	样本类型 Type	芳基类 Aryl-	烷基类 Alkyl-				含氯类 Chlorinated-			参考文献 Reference
						DPHP	DEP	DnBP	BEHP	BBOEP	BCEP	BCIPP	BDCIPP	
	2016	儿童	0—5	227	尿液	250	—	—	—	50	670	810	80	Zhang等[72]
	2015	成人		306	尿液	400	—	—	—	100	1000	200	6200	Ding等[67]
	2015*	儿童	6—14	411	尿液	280	—	120	—	50	1040	150	50	Chen等[73]
	2015*	怀孕妇女	—	23	尿液	1100	—	—	—	—	—	—	1200	Feng等[74]
	2014	成人和儿童	0.4—87	221	尿液	550	—	290	—	65	720	94	91	Lu等[42]
	2014—2016	孕妇	28.8±4.3	113	尿液	220	—	—	—	50	—	—	120	Luo等[34]
	—	儿童	12—15	306	尿液	420	—	—	—	N.D.	1000	180	6170	丁锦建等[75]
美国	2018	成人	33.8±12	213	尿液	1060	348	16.8	13.4	32.6	354	83.8	414	Wang等[76]
	2015	母亲	—	28	尿液	1200	—	—	—	—	—	—	3300	Butt等[77]
		子女	2—70个月	33	尿液	2900	—	—	—	—	—	—	10900	
	2015	成人	—	76	尿液	890	—	—	—	—	N.D.	N.D.	690	Jayatilaka等[78]
	2010—2011	消防员	—	146	尿液	2900	—	—	—	—	860	240	3400	
	2013—2014	母亲	—	22	尿液	1900	—	—	—	—	—	N.D.	2400	Butt等[79]
		子女	—	26	尿液	3000	—	—	—	—	—	N.D.	5600	
	2013—2014	儿童	15—18个月	21	尿液	3370	—	—	—	—	—	—	6810	Thomas等[80]
		儿童	—	20	尿液	8150	—	—	—	—	—	—	2700	
	—	成人	—	13	尿液	1500					3400	400	2500	Pretropoulou等[68]
	2011—2012	孕妇	28—36	39	尿液	1900	—	—	—	—	—	—	1300	Hoffman等[81]
	2011	成人	—	16	尿液	440	—	110	—	N.D.	630	N.D.	90	Dodson等[82]
	2011	成人	23—46	9	尿液	2974	—	—	—	—	—	—	410	Cooper等[83]
	2010—2011	成人	40±12.7	47	尿液	2990	—	—	—	—	—	—	—	Preston等[84]
				46	尿液	1800	—	—	—	—	—	—	—	
				42	尿液	2110	—	—	—	—	—	—	—	
	2009	成人	49*	29	尿液	—	—	—	—	—	—	—	408	Carignan等[85]
	2008*	母亲	32.6±4.1	96	尿液	2500	—	—	—	—	—	700	1100	Gibson等[86]
		儿童	4.8±0.8	90	尿液	3200	—	—	—	—	—	900	2600	
	2002—2007	成年男性	18—54	61	尿液	310	—	—	—	—	—	—	130	Meeker等[87]
	2000—2001	孕妇	26	310	尿液	930	—	—	—	—	—	N.D.[b]	280	Castorina等[88]
澳大利亚	2010—2013	成人和儿童	—	72 23	尿液	24400 63400	— —	— —	— —	<LOQ N.D.	— —	— —	1000 660	van den Eede等[65]
波多黎哥	2011—2015	孕妇	18—40	141	尿液	15100	—	—	—	—	1120	260	1150	Ingle等[89]
加拿大	2014	成人	—	12	尿液	N.D.—1290	—	N.D.	N.D.	N.D.	N.D.—12330	N.D.—680	N.D.—1170	Su等[69]
	2010—2012	孕妇	18—45	24	尿液	2880	—	—	—	380	<LOQ	<LOQ	270	Kosarac等[90]
挪威	2015*	母亲	32—54	244	尿液	630	—	N.D.	—	N.D.	—	—	80	Cequier等[91]
		子女	6—12	112	尿液	1000	—	N.D.	—	N.D.	—	—	230	
	2013—2014*	成人	—	55	头发	24000	—	<LOQ	—	—	—	—	<LOQ	Xu等[66]
			—	61	尿液	610	—	99	—	<35	—	—	68	

[a] 收集样本数, the number of collected samples; [b] N.D.: 未检出, N.D. this chemical was not detected in all samples; [c] <LOQ: 小于定量限, geometric mean or median concentration was lower than the limit of quantification ; — 没有数据, data unavailable; * 暴露水平为中位数, the concentration was shown by median

表 2　主要 tri-OPEs 的国内外人群平均内暴露水平

Table 2　Typical tri- OPEs levels among population reported in various studies worldwide

国家或地区 Sample site	年份 Time	年龄/岁 Year	数量^a *n*	类型 Type	芳基类 Aryl-			烷基类 Alkyl-				含氯类 Chlorinated-			单位 Unit	参考文献 Reference
					TPHP	TMPP	EHDPP	TEP	TnBP	TEHP	TBOEP	TCEP	TCIPP	TDCIPP		
中国	2019	29—94	232	血浆	N.D.^{b}	0.79	0.72	1.1	N.D.	N.D.	—	—	N.D.	—	μg·L^{-1}	Li等[92]
			56	血浆	6.01	N.D.	N.D.	0.16	0.88	N.D.	—	—	N.D.	—	μg·L^{-1}	
	2018*	17—87	57	全血	0.366	—	1.100	0.432	0.176	<0.145	0.164	<0.194	<0.166	<0.393	ng·mL^{-1}	Hou等[62]
			57	血清	<0.307	—	0.933	0.196	0.154	<0.145	0.209	<0.194	1.05	<0.393	ng·mL^{-1}	
			52	尿液	<0.061	<0.002	<0.016	0.075	<0.006	<0.091	0.038	<0.039	<0.033	<0.079	ng·mL^{-1}	
	2018	22—88	89	血清	10.2	—	—	—	10.3	—	—	227	1.0	—	ng·g^{-1} lw^d	Gao等[93]
	2015	—	9	血清	<4.2	—	—	—	3.4—46.5	—	—	248.6—958.2	—	—	ng·g^{-1} lw	Li等[94]
	2013*	18—87	99	血液	0.35	—	0.85	0.15	N.D.	N.D.	0.05	0.1	0.05	N.D.	ng·mL^{-1}	Ya等[95]
	2012*	20—50	257	全血	0.43	0.09	1.22	0.49	37.8	0.04	0.54	<0.31	0.71	N.D.	ng·mL^{-1}	Zhao等[96]
	2005*	18—37	50	胎盘	15.1	—	N.D.	10.2	N.D.	N.D.	16.7	142	—	N.D.	ng·g^{-1}lw	Ding等[64]
挪威	2012	32—56	48	头发	52	—	27	—	22	12	65	72	—	30	ng·g^{-1}	Kucharska等[64]
		6—12	54	头发	63	—	21	—	11	8	318	59	—			
美国	2009—2012	19—40	100	母乳	0.149	0.021	0.022	0.350	0.539	0.245	1.44	0.036	0.221	—	ng·mL^{-1}	Ma等[97]
日本*	2009—2011	25—42	20	母乳	1.4	N.D.	N.D.	N.D.	0.39	—	0.24	0.14	—	N.D.	ng·g^{-1} lw	Kim等[51]
菲律宾*	2008	17—45	41	母乳	19	2.3	N.D.	N.D.	1.5	—	N.D.	42	—	N.D.	ng·g^{-1} lw	
越南*	2008	21—34	26	母乳	4.9	0.28	N.D.	N.D.	2.0	—	N.D.	N.D.	—	N.D.	ng·g^{-1} lw	
瑞典*	—	—	—	母乳	8.5	—	6.5	—	12	—	4.7	4.9	—	4.3	ng·g^{-1} lw	Sundkvist等[52]

[a] 收集样本数, the number of collected samples; [b] N.D.: 未检出, N.D. this chemical was not detected in all samples; [c] <LOQ: 小于定量限, geometric mean or median concentration was lower than the limit of quantification ; [d] lw: lipid weight ; — 没有数据, data unavailable; * 暴露水平为中位数, the concentration was shown by median.

1.3　人群 OPEs 暴露特征

人群 OPEs 暴露存在明显地域差异. 以 DPHP 为例, 澳大利亚人浓度水平高达 63400 pg·mL^{-1}[65], 其次是挪威成年人 (24000 pg·mL^{-1}) [66]. 中国和美国人群普遍检出 DPHP, 但是美国人浓度水平 (8150 pg·mL^{-1}) 要高于中国人 (1200 pg·mL^{-1})（见表 1）. 就 OPEs 类型而言, 世界各国人群普遍暴露于芳基类和含氯类 OPEs. 章涛等研究了中国 14 个省市普通人群和儿童尿样中 8 种 OPEs 代谢产物, 发现中国居民普遍暴露于 OPEs, 在 10 个省、市中人群暴露以氯代 OPEs 为主, 4 个地区以非氯代 OPEs 暴露为主[29]. Ding 等检测成年人尿液 OPEs 代谢产物水平, 结果显示一般成年人均暴露于多种氯代 OPEs, 尤其是磷酸二 (1,3-二氯异丙基) 酯 [Bris(1,3-dichloroisopropyl) phosphate, BDCIPP] 暴露水平高 (6200 pg·mL^{-1}), 远高于 DPHP 含量水平 (400 pg·mL^{-1}) [67]; Petropoulou 等检测美国成年人尿液中 4 种 OPEs 代谢物含量水平, 发现 3 种氯代 OPEs, 尤其是磷酸二（2-氯乙基）酯 [Bri(2-chloroethyl) phosphate, BCEP] 暴露水平较高, 约为 DPHP 含量水平的 2 倍[80]. Su 等检测加拿大成年人尿液也发现 3 种氯代 OPEs, 其中磷酸二 (2-氯乙基) 酯 [Bis(2-chloroethyl) phosphate, BCEP] 的浓度水平最高 (12330 pg·mL^{-1}), 接近 DPHP 含量水平的 10 倍[69]. 但是, 澳大利亚成年人尿液样本中 DPHP 含量水平 (63400 pg·mL^{-1}) 远高于含氯类 OPEs(660 pg·mL^{-1}) [65].

烷基类 OPEs 暴露仅见中国人群报道最多, 其次是美国和挪威人群 (见表 1).

人群 OPEs 暴露特征与年龄、职业密切相关. Hu 等在评估中国广州地区经呼吸道摄入(室内和室外环境)的 OPEs 暴露风险时发现, 成年人是危害熵(Hazard Quotient, HQ)和终身致癌风险(Incremental life cancer risk, ILCR)最高的人群, 紧接着是青少年和儿童, 最低的为老年人[98]. 但是, van den Eede 等分析澳大利亚居民尿样中 9 种 di-OPEs, 结果显示, di-OPEs 浓度水平与年龄呈负相关, 且儿童中 DPHP 和 BDCIPP 的浓度显著高于成人水平, 提示儿童是某些类别 OPEs 的高暴露人群[65]. Chen 等检测中国儿童尿液 OPEs 代谢产物, 结果发现 BCEP 的检出率和浓度最高, 而 DPHP 次之, 说明中国儿童以氯代和芳基类 OPEs 暴露为主[73]. Cequier 等发现挪威子女尿液中 4 种二烷基和二芳基有机磷酸(Dialkyl and diaryl phosphates, DAPs)的浓度远高于母亲, 提示当地儿童对于烷基 OPEs 和芳基 OPEs 的暴露比较敏感[93]. 针对孕妇人群, Hoffman 等分析美国孕妇尿液, 结果显示 DPHP 与 BDCIPP 检出率相同(97.4%)[81], 前者含量水平略高于后者; 而 Feng 等检测我国孕妇尿液, 发现 BDCIPP 检出率仅 17% 而 DPHP 全部可检出, 两者含量水平分布相近[74]. Shi 等分析某电子垃圾回收处理场附近成年工人和儿童尿液标本, 结果显示, 儿童有比成人更低的 di-OPEs 暴露水平, 提示成年人的职业 OPEs 暴露风险不容忽视[23].

OPEs 在过去数十年在产量和用量上正快速增长, 大量的研究数据表明人群暴露的形势越来越严峻, 暴露的 OPEs 种类越来越多, 浓度值也呈现递增趋势. Hoffman 等收集了近 10 年本实验室进行的 14 项关于 OPEs 的流行病学研究发现[99], 尿液种 TDCIPP 的代谢产物 BDCIPP 自 2002 年起始呈急剧增长态势, 仅 2014—2015 年比过去 10 年浓度水平增长 15 倍之多, TPHP 的代谢产物 DPHP 也增速迅猛. 随着暴露量增加, 对人群健康危害问题迫切需要关注.

1.4 人群 OPEs 健康风险评估

目前大部分研究, 都以美国国家环境保护局(U.S. Environmental Protection Agency, USEPA)建立的人体暴露评估模型[100] 和已有的文献[26, 101－102] 中获得参数, 以计算 OPEs 的暴露量, 具体计算公式如下:

呼吸吸入途径: $\mathrm{EDI_A}=C_{\mathrm{Air}}\times\mathrm{IR}\times\mathrm{IEF}/\mathrm{BW}$

式中, $\mathrm{EDI_A}$ 为空气中 OPEs 通过呼吸的日摄入量估算值, $\mathrm{ng\cdot kg^{-1}\cdot d^{-1}bw}$; C_{Air} 为空气(气态和颗粒态)中 OPEs 浓度, $\mathrm{ng\cdot m^{-3}}$; IR 为室内空气日吸收速率, $\mathrm{m^3\cdot d^{-1}}$; IEF 为日暴露比率, 无量纲; BW 为体重, kg.

经口摄入途径: $\mathrm{EDI_D}=C_{\mathrm{Dust}}\times\mathrm{IR}\times\mathrm{IEF}/\mathrm{BW}$

式中, $\mathrm{EDI_D}$ 为粉尘中 OPEs 通过经口摄入的日摄入量估算值, $\mathrm{ng\cdot kg^{-1}\cdot d^{-1}bw}$; C_{Dust} 为粉尘中 OPEs 浓度, $\mathrm{ng\cdot g^{-3}}$; IR 为粉尘中 OPEs 日吸收速率, $\mathrm{g\cdot d^{-1}}$; IEF 为日暴露比率, 无量纲; BW 为体重, kg.

皮肤吸收途径: $\mathrm{EDI_{DA}} = 10\times C_{\mathrm{Dust}}\times\mathrm{BSA}\times\mathrm{SAS}\times\mathrm{ABS}\times\mathrm{IEF}/\mathrm{BW}$

式中, $\mathrm{EDI_{DA}}$ 为灰尘中 OPEs 通过皮肤吸收的日摄入量估算值, $\mathrm{ng\cdot kg^{-1}\cdot d^{-1}bw}$; BSA 为暴露在环境中的皮肤面积, $\mathrm{m^2}$; SAS 为皮肤对灰尘的吸附系数, $\mathrm{mg\cdot cm^{-2}\cdot d^{-1}}$; ABS 为皮肤对灰尘中 OPEs 的吸收系数, 无量纲.

OPE 的环境持留性和食物链的生物放大效应不如 PBDEs 强烈, 但 OPEs 在世界范围内被持续大量使用, OPEs 在人群膳食中普遍存在. 人平均每日摄入量 DI 计算公式如下:

$$\mathrm{DI} = \sum(C_i\times \mathrm{CF}_i)/\mathrm{BW}$$

式中, C_i 为食品中 OPEs 的中位浓度; CF_i 为食品每日消耗量(中位数), $\mathrm{ng\cdot kg^{-1}\cdot\ d^{-1}bw}$

评估人群 OPEs 暴露风险的危险熵值(Hazard quotient, HQ)计算公式如下:

$$\mathrm{HQ} = \mathrm{DI}/\mathrm{RfD}$$

其中, RfD 用于描述每种 OPEs 的参考剂量 (Reference dose, RfD), 既往文献 [102 − 107] 中和 USEPA (2017 年)修订提供相关毒理学参数(见表 3). 当 HQ≥1 时, 认为具有健康风险. 每种 OPEs 的 HQ 总和为危险指数(Hazard index, HI), 计算公式如下:

$$\mathrm{HI} = \sum \mathrm{HQ}$$

表 3　OPEs 毒理学参数

Table 3　Toxicological parameters of OPEs

	RfD[41][a]	RfD[104][a]	RfD[100][a]	SFO[100][b]	GIABS[100][c]	ABS[102][d]
TMP	—	—	0.01	0.02	1	0.1
TnBP	0.0024	0.024	0.01	0.009	1	0.1
TCIPP	0.008	0.008	0.01	—	1	0.1
TCEP	0.0022	0.0022	0.007	0.020	1	0.1
TDCIPP	0.0015	0.0015	0.02	—	1	0.1
TBOEP	0.0015	0.0015	—	—	—	—
TDBPP	—	—	—	2.300	1	—
TEHP	—	—	0.1	0.0032	1	0.1
TPHP	0.007	0.007	—	—	—	—
TMPP	0.0013	0.0013	0.02	—	—	—
DMMP	—	—	0.06	0.001	1	0.1

[a] 为参考剂量($\mathrm{ng\cdot kg^{-1}\cdot d^{-1}bw}$); [b] 经口风险斜坡因子[$\mathrm{1/(ng\cdot kg^{-1}\cdot d^{-1}bw)}$]; [c] 胃肠道吸收因子; [d] 皮肤吸附分数.

Li 等[103] 完善了 OPEs 的风险评估模型, 提出计算通过摄入和皮肤接触暴露于室内灰尘中 OPEs 的慢性摄入量(Chronic daily intake, CDI)公式如下:

$$\mathrm{CDI_{ingestion}} = (C_i \times \mathrm{IR} \times \mathrm{ED} \times \mathrm{EF} \times \mathrm{CF})/(\mathrm{AT} \times \mathrm{BW})$$

$$\mathrm{CDI_{dermal\ contact}} = (C_i \times \mathrm{ED} \times \mathrm{EF} \times \mathrm{SA} \times \mathrm{AF} \times ABS \times \mathrm{CF})/(\mathrm{AT} \times \mathrm{BW})$$

其中, $\mathrm{CDI_{ingestion}}$ 为室内灰尘的摄入相关的每日摄入量 [$\mathrm{mg\cdot(kg\cdot d)^{-1}}$], $\mathrm{CDI_{dermal\ contact}}$ 为皮肤接触灰尘摄入相关的每日摄入量 [$\mathrm{mg\cdot(kg\cdot d)^{-1}}$], C_i 为某种 OPEs 浓度($\mathrm{mg\cdot kg^{-1}}$), IR 为室内灰尘的摄入率($\mathrm{mg\cdot d^{-1}}$), ED 为持续暴露时间(a), EF 为暴露频率($\mathrm{d\cdot a^{-1}}$), CF 为转换因子($\mathrm{0.01\ g\cdot mg^{-1}}$), SA 为与灰尘接触的皮肤表面积($\mathrm{cm^2}$), AF 为皮肤黏附因子($\mathrm{mg\cdot m^{-2}}$).

非致癌风险评估基于危险系数(HI)和危险熵值(HQ), 对于通过意外摄入和皮肤接触暴露于多种 OPEs 的风险, 计算公式如下:

$$\mathrm{CR} = \mathrm{CR_{ingestion}} + \mathrm{CR_{dermal\ contact}} = \sum_{i=1}^{n}[\mathrm{CDI_{ingestion}}/\mathrm{RfD_i} + \mathrm{CDI_{dermal\ contact}}/(\mathrm{RfD_i} \times \mathrm{GIASB_i})]$$

致癌风险的计算公式如下:

$$\mathrm{CR} = \mathrm{CR_{ingestion}} + \mathrm{CR_{dermal\ contact}} = \sum_{i=1}^{n}[\mathrm{CDI_{ingestion}} \times \mathrm{SFO_i} + \mathrm{CDI_{dermal\ contact}} \times \mathrm{SFO_i}/\mathrm{GIASB_i})]$$

SFO 为经口风险斜坡因子(oral cancer slope factor, SFO)

2　OPEs 的甲状腺毒性(Toxicities of OPEs in thyroid)

环境污染物的甲状腺毒性通常指污染物通过改变甲状腺及其所分泌的甲状腺激素水平而产生的生物毒性. 甲状腺激素在促进生长发育和调控产热及物质代谢方面起重要作用, 又在调节人体中枢神经系统发育和维持神经系统功能等方面发挥至关重要的作用. 甲状腺受神经-内分泌系统共同调节, 与下丘脑和垂体构成下丘脑-垂体-甲状腺轴 (hypothalamus-pituitary-thyroid axis, HPT) 体系, 并通过 HPT 轴对甲状腺激素稳态进行动态调节. OPEs 暴露引起甲状腺毒性, 其对 HPT 轴体系可能的作用模式 (mode of action, MOA) 包括: ①OPEs 直接作用于甲状腺组织, 产生甲状腺腺体损伤, 即暴露-甲状腺组织-肿瘤; ②OPEs 影响控制递送甲状腺激素到靶细胞或组织的蛋白, 或者干扰肝脏代谢和胆汁排泄, 影响甲状腺激素的合成、转运、结合和代谢等过程, 从而干扰甲状腺激素内环境的稳态, 继而改变循环血中甲状腺激素水平, 导致产生不良健康效应, 即暴露-激素稳态-效应.

2.1　OPEs 暴露-甲状腺组织-肿瘤的作用模式

OPEs 暴露对甲状腺的损伤主要表现在甲状腺组织形态学的改变和甲状腺肿瘤的发生. 已有动物实验显示, 给 SD 大鼠每天染毒 TDCPP（80 $mg\cdot kg^{-1}$ bw）, 12 个月和 24 个月后雌性和雄性大鼠均出现甲状腺重量增加, 而且雌性大鼠的甲状腺腺瘤发生率提高, 甲状滤泡旁细胞瘤发生率也略微上升; 给 F-344 大鼠每周 5 d 染毒 TCEP（88 $mg\cdot kg^{-1}$ bw）, 103 周后雄性大鼠的甲状腺滤泡腺瘤发生率略有上升[31]. 一项人群流行病学研究发现, 人暴露于室内灰尘中高浓度 TCEP 与甲状腺乳头状癌发生呈正关联 [OR=2.42（1.10, 5.33）, P=0.03], 而暴露于室内灰尘中高浓度 TPHP 仅与较低恶性程度的人甲状腺乳头状癌发生呈正关联 [OR=3.63（1.26, 10.4）, $P<0.05$][106]. 但是, 另一项人群病例-对照研究显示, 尿液中 DPHP、BCIPP、BDCIPP、BCIPHIPP 等 di-OPEs 浓度水平与人甲状腺癌患病风险无关联[37]. 可见, 研究结论存在不一致.

2.2　OPEs 暴露-激素稳态-效应的作用模式

通过影响 THP 轴来改变生物体甲状腺激素稳态是 OPEs 暴露产生不良健康效应重要作用模式. 这里的甲状腺激素包括 3,5,3′,5′-四碘甲状腺原氨酸,即甲状腺素（Thyroxine, T4）、3,5,3′-三碘甲状腺原氨酸（3,5,3′-triiodothyronine, T3）、促甲状腺激素释放激素（Thyortropin releasing hormone, TRH）、促甲状腺激素（Thyroid stimulating hormone, TSH）、血清游离 3,5,3′,5′-四碘甲状腺原氨酸,即甲状腺素（free thyroxine, fT4）和游离 3,5,3′-三碘甲状腺原氨酸（free 3,5,3′-triiodothyronine, fT3）、血清总 3,5,3′,5′-四碘甲状腺原氨酸（total thyroxine, tT4）和总 3,5,3′-三碘甲状腺原氨酸（total 3,5,3′-triiodothyronine, tT3）等. 关于 OPEs 暴露对于各种生物体甲状腺激素水平的影响目前仍然存在较大的争议（表 4）.

表 4　OPEs 暴露与甲状腺激素水平的变化

Table 4　OPEs exposure and changes in thyroid hormone levels

出版时间 Time	目标化合物 Compound	研究对象 Subject	研究结果 Result	染毒情况 Dose	参考文献 Reference
2013	TDCPP	斑马鱼	仔鱼T4↓T3↑	10—600 $\mu g\cdot L^{-1}$, 144 h	Wang等[107]
2015	TDCPP	斑马鱼	F0代雌鱼T3↓T4↓ F1代T4↓	0—100 $\mu g\cdot L^{-1}$, 6 个月	Wang等[110]
2015	TPHP	斑马鱼	仔鱼T3↑T4↑	40—500 $\mu g\cdot L^{-1}$, 7 d	Kim等[108]
2017	TBOEP	斑马鱼	仔鱼T3↑T4↑	0—2000 $\mu g\cdot L^{-1}$, 144 h	Liu等[109]
2019	TDCPP, TPP	斑马鱼	T3↓T4↓(雄鱼), T3↑T4↑(雌鱼)	0—1000 $\mu g\cdot L^{-1}$, 14 d	Liu等[111]
2013	TCIPP	鸡胚	fT4↓	0—51600 $ng\cdot g^{-1}$, 22 d	Farhat等[112]
2013	TDCIPP	鸡胚	fT4→	0—45000 $ng\cdot g^{-1}$, 22 d	Farhat等[112]
2014	TEP	鸡胚	fT4↓TT4→	8—241500 $ng\cdot g^{-1}$, 22 d	Egloff等[113]
2016	TDCIPP	大鼠	T3↑TT4→ fT4→	50—250 $mg\cdot kg^{-1}$, 21 d	Zhao等[114]
2010	TDCPP	室内灰尘	fT4↓（男性）	—	Meeker等[120]
2013	TDCIPP、TPHP、BDCIPP、DPHP	男性尿液	TT3↑TSH↑fT4→	—	Meeker等[119]
2017	DPHP	人尿液	TT4↑FT4→TT3→TSH→	—	Preston等[84]

斑马鱼是研究最多的受试生物. 将斑马鱼胚胎暴露于不同浓度的 TDCPP, 结果发现, 仔鱼 T4 的含量显著降低, 而 T3 含量升高[107]; 但是将斑马鱼暴露于 TPHP, 仔鱼体内 T3 和 T4 含量均显著增加[111]. 较低剂量 TBOEP（0— 2000 $\mu g\cdot L^{-1}$）暴露也显著增加了斑马鱼仔鱼体内 T3 和 T4 的含量, 会使斑马鱼胚胎畸形率增加, 发育延缓及心率降低[109]. OPEs 暴露还表现出性别差异. 雌性斑马鱼对 TDCPP 暴露敏感, 能在脑组织蓄积 TDCPP; 长期暴露于低浓度 TDCPP 会改变雌性鱼体中枢神经系统基因表达, 导致神经行为毒性作用[113]. 最近研究发现, 将斑马鱼暴露于 TDCPP 和 TPHP 在 14d 后, 雄鱼血浆 T3 和 T4 水平显著降低而雌鱼升高, 这与暴露改变了 HPT 轴相关基因表达有关; TDCPP 和 TPHP 暴露引起雄鱼脑组织中促肾上腺皮质激素释放激素 (Corticotropin-releasing hormone, CRH) 和 TSH 转录水平上调, 但是雌鱼体内 CRH 和 TSH 表达下调; 同时雄鱼的甲状腺和肝脏组织中甲状腺球蛋白 (Thyroglobulin, Tg) 和脱碘酶 (Deiodinase type 2, DIO2) 表达下调[111].

就鸟类而言, TDCIPP 处理组中鸡胚血清 fT4 含量显著降低[112], TEP 处理组呈现类似结果[113], 但是在 TCIPP 处理组中血清 fT4 水平没有显著变化. 在哺乳动物实验研究中, TDCIPP 暴露显著上调了大鼠的脱碘酶 (Deiodinase type 1, DIO1)、甲状腺素运载蛋白 (Transthyretin, TTR)、甲状腺激素清除酶 (Udp-glucuronosyltransferase-1A6, UGT1A6) 以及甲状腺激素合成相关基因 (NIS, TPO 及 Tg) 的表达, 引起大鼠血清中 T3 的浓度显著升高, 但不影响 tT4 和 fT4 的含量, 这提示 TDCIPP 暴露能影响 HPT 轴体系中与甲状腺激素的合成、转运、代谢以及清除、反馈等蛋白的基因表达, 从而导致甲状腺功能紊乱[117].

相对于传统的整体生物实验, 离体生物实验使暴露后效应变化更容易判别与获取. 体外细胞研究表明, 将大鼠垂体瘤细胞 (Rat pituitary cell lines, GH3) 暴露于一定剂量的 TPHP, 处理 48 h 后在 TPHP 暴露组中促甲状腺释放激素基因的表达显著增加; 进一步用 TPHP 处理大鼠甲状腺囊泡细胞 (Thyroid follicular cell lines, FRTL-5)24 h 后, TPHP 暴露组中钠碘转运体 (Sodium iodide symporter, NIS) 及甲状腺过氧化物酶基因 (Thyroid peroxidase, TPO) 的表达显著增加, 这说明 TPHP 直接作用于脑垂体细胞及甲状腺滤泡刺激甲状腺激素的合成.

OPEs 暴露可能还通过干扰生长激素或性激素水平, 间接发挥发育毒性效应. 一项动物试验显示, 将斑马鱼幼鱼暴露于环境相关剂量的 TDCIPP（$6300\ \mathrm{ng\cdot L^{-1}}$）在 120 d 后, 雌性斑马鱼的体长变短、体指数和性腺指数均显著下降, 并引起生长激素/胰岛素样生长因子（GH/IGF）轴相关基因表达下调, 后者显著影响幼体生长[115].

甲状腺激素主要是通过细胞中甲状腺激素受体 (Thyroid hormone receptor, TR) 发挥作用. 人的 TR 由 TRα 和 TRβ 两个基因编码, 产生 TRα1、α2、TRβ1、β2 等异构体. 在 T3 作用下, TR 与称作 T3 依赖性辅激活蛋白的蛋白结合促进转录, 在 T3 不存在的情况下与协同抑制因子结合, 发挥抑制目的基因转录活化的作用. 陆美娅等通过 TRβ 介导的报告基因实验检测发现, 9 种 OPEs（TBP、TCP、TPP、TBOEP、TCEP、TDCIPP、TCIPP、TBPP 和 TEHP）均无激动活性, 而其中 4 种则表现出显著的抗甲状腺激素效应, 活性的大小顺序为 TCP>TBP>TCIPP>TDCIPP; 分子对接结果表明, OPEs 甲状腺激素活性的强弱程度, 取决于它和 TRβ 不同的结合方式, 结构中含有苯环、卤素及短链的 OPEs 可能更容易表现出拮抗效应[116]. Ren 等通过体外细胞增殖实验和荧光素酶报告基因实验, 评估了 4 种 OPEs(TMP、TEP、TCEP 和 TDCIPP) 对 TRα/β 活性的影响, 发现 TDCPP 能够更有效地结合配体结合区 (ligand-binding domain, TRβ-LBD), 对 TRβ 产生明显的拮抗活性[123]. Zhang 等通过荧光素酶报告基因发现 4 种 OPEs(TDCIPP、TCIPP、TnBP 和 TMPP) 对 TRβ 活性有拮抗作用, 且拮抗作用逐渐增强, 即拮抗活性 TDCIPP<TCIPP<TnBP <TMPP [118]. 目前人群流行病学研究资料十分有限. Preston 等分别在同年的 1、6、12 月检测了 51 名成年人尿液中 DPHP 浓度和血液甲状腺功能相关激素, 发现 DPHP 的浓度与血清中 FT4、TT3 和 TSH 没有显著相关性, 仅与 TT4 水平升高相关 [84]. Meeker 等也发现室内灰尘中 TDCPP 的浓度与男性血液 fT4 的浓度呈显著负相关[87]. 另一项研究检测男性尿液中 TDCIPP、TPHP 及其代谢产物 BDCIPP 和 DPHP, 发现尿液中 BDCIPP 和 DPHP 的浓度与血清中 TT3 含量呈正相关, 而且尿液中 BDCIPP 浓度与体内 TSH 的含量呈正相关[119], 而与血清 fT4 没有显著相关.

甲状腺激素是维持胎儿和新生儿正常生长发育的关键激素. OPEs 暴露通过改变甲状腺激素水平, 间接产生发育神经毒性作用[35]. 人群流行病学研究发现, 美国孕妇尿液中 TPHP 浓度每增加 10 倍, 出生后 7 岁儿童的 IQ 减少 2.9 分（CI:−6.3, 0.5）以及学习记忆减少 3.9 分（CI:−7.3—−0.5）[36]; 中国孕妇尿液中 DPHP 高负荷水平与女性新生儿低出生体重风险有显著的相关性（$P<0.05$）; 这些提示 TPHP/DPHP 暴露可能会影响子代神经发育以及产生出生缺陷[34].

3　问题与展望（Question and prospects）

迄今为止, 关于 OPEs 的人群暴露特征及其甲状腺毒性的相关研究受到热切关注, 未来亟需研究和解决的问题和挑战有:

（1）人群 OPEs 暴露评估方法比较单一. 大部分人群暴露研究来自点尿样, 易受采样时间、污染物代谢动力学差异等因素影响, 造成暴露评估不确定性较高. OPEs 体内代谢过程复杂, 一些羟基化代谢产物例如 4-OH-TPHP 已被报道[123], 且一些 OPEs 例如 TCEP 在体内代谢效率较低, 更多以原型形式排泄[52], 仅用 di-OPEs 作为尿液暴露标志, 容易低估人群暴露风险, 需要筛选新型暴露生物标志和合适的

生物监测手段,以便真实全面地反映 OPEs 的人体负荷水平. 另外,环境介质中 OPEs 赋存水平研究较多,但人群 OPEs 内暴露特征研究较少,而涉及 OPEs 内外暴露关联的研究鲜见报道,在完成定量检测的同时也要合理建立内外暴露剂量之间的关系,需开展生理毒物代谢动力学(PBTK)模型研究.

(2)OPEs 暴露对哺乳动物甲状腺内分泌系统危害的研究非常有限. 目前动物试验研究的暴露途经单一,暴露剂量一般较高. 而人类可从多种媒介中暴露于低浓度的 OPEs. 因此,需要关注不同暴露途径,如灰尘吸入、皮肤接触暴露等,在长期低剂量下,同时考虑不同暴露敏感期,以准确评估 OPEs 的甲状腺毒性.

(3)甲状腺毒性作用机制研究有待深入探究. 目前研究的观察指标仅是甲状腺激素的升高或者下降,以及相关的 HPT 轴调控基因表达改变等,缺少对 OPEs 暴露与甲状腺肿瘤发生的分子机制深入探究. 需要深入研究 OPEs 暴露影响子代甲状腺内分泌系统的作用机制,从而阐释 OPEs 暴露对儿童神经发育毒性作用机制.

(4)OPEs 与其他污染物的相互作用报道较少. OPEs 在环境中并不是单一存在的,由于具有环境持久性和高生物蓄积性,PBDEs 以及有相似结构的 PCBs 在我国仍然广泛存在于环境中[124]. 例如,Hoffman 等人同时检测 TPHP 和 BDE-47[108]. 但目前缺乏对 OPEs 与其他污染物的联合暴露毒性作用的研究,尤其是模拟真实环境下低浓度、长时间、联合暴露毒效应的研究.

(5)有关 OPEs 环境污染的人体健康危害流行病学研究缺乏. 当前,我国关于 OPEs 健康风险评估研究更多在环境赋存水平检测,反映人体暴露水平的数据有限,更缺乏探究健康危害的人群流行病学研究数据. 对于这样一种在我国使用量正日益增大的新型环境污染物,亟待深入开展 OPEs 的人群流行病学研究,对于准确评估我国人群 OPEs 暴露的潜在健康风险具有重要意义. 目前 OPEs 现有的毒理学数据尚不完全,应填补暴露和风险评估之间的空白,高度重视相关风险管理、制定环境安全阈值,出台政策法规以限制部分 OPEs 的过度使用,保护人类健康和环境的可持续发展.

(6)OPEs 具有可降解性,在评价膳食暴露时,应将烹饪方式也纳入考量,若能在同一队列中分析膳食暴露和 OPEs 及其代谢产物,也须制定符合中国国情的健康指导值,有助于理解不同 OPEs 人体负荷的暴露途径.

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