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新型全氟及多氟聚醚羧酸识别、分布特征及毒理效应研究进展

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摘要 随着全氟辛酸(PFOA)的管控, 工业中开始使用结构中含有醚氧键的全氟及多氟聚醚羧酸(PFECA)作为加工助剂替代PFOA. 近年来, 得益于非靶向筛查和靶向分析技术的快速发展, 不同环境介质和生物样品中已陆续检出多种PFECA, 浓度呈升高趋势. 已有研究发现, 六氟环氧丙烷三聚体(HFPO-TA)、六氟环氧丙烷四聚体(HFPO-TeA)等PFECA表现出较PFOA更强的生物累积和毒性效应. 相较于传统全氟及多氟烷基物质(PFAS), PFECA结构更为复杂, 对环境和生物体的危害机制也可能存在差异. 本文围绕PFECA的结构种类、污染水平和毒性效应, 从非靶向识别、环境行为、生物及人群暴露水平、毒性效应和分子机制等多个方面对近年来的相关研究进行概述, 探讨当前PFECA应用中存在的问题和潜在风险, 对未来的研究方向和应用前景进行展望, 旨在为PFAS替代品的环境污染及风险评估提供参考, 为我国开展PFAS的管控和削减行动提供支撑.

关键词 PFECA, 非靶向识别, 环境行为, 人体暴露, 毒性效应

据不完全统计, 全球投入生产和使用的化学品种类已有超35万种之多[1,2]. 这些化学物质在生产、加工使用、消费和废弃处置的全过程都有可能排放到环境中. 此外, 还有众多无意产生的污染物和化工产品的降解产物. 我国是化学品生产和使用大国, 目前化学品销售量已经超过了欧美的总和, 成为世界最大的化工市场[3].

全氟及多氟烷基物质(PFAS)多氟烷基物质(PFAS)是一类碳骨架上的氢原子全部或部分被氟原子替代, 呈现高度氟化的、人工合成有机物[4]. PFAS具有强的碳-氟共价键(C–F键), 因此, 此类化合物具有耐酸碱、耐氧化, 耐热等特性; 由于其极化率低, 这些化合物折射率、介电常数和表面张力都变小; 另外, PFAS化合物分子间力弱, 沸点和熔点低, 摩擦力小, 黏度低, 具有疏水、疏油的特性. 由于PFAS具有上述独特理化性质, 因而被广泛地应用于人类衣、食、住、行诸多方面(如纺织、户外服、不粘锅、食品包装、家具涂料、航空液压油、燃料电池等), 目前在化工和民生领域具有不可或缺性. 正是PFAS化合物中具有高键能C–F键(以CF_4为例, 其键能约为546.2 kJ/mol), 因此, 此类化合物难以水解、光解和被微生物降解, 近年来的研究显示传统长链PFAS(全氟碳原子数 ⩾ 6)在环境中持久存在且具有高的生物累积性和生物毒性[5~9]. PFAS已在全球环境介质和生物体中广泛检出[10~13], 甚至人体不同组织液(如血清、脐带血、胎盘、精浆、脑脊液、母乳等)中也检出不同链长及异构体的PFAS[11~14]. 流行病学研究发现, 部分PFAS在人体中的暴露水平与多种生化和生理指标的改变存在显著正相关, 如肾癌

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和睾丸癌[15]、高胆固醇[16]、甲状腺机能减退[17]等. 动物模型研究发现PFAS具有肝毒性、神经毒性、生殖发育毒性、免疫毒性以及内分泌干扰效应[18,19]等多种毒性.

鉴于长链PFAS具有环境持久性、生物累积性、长距离迁移以及多种毒性效应, 对全球生态环境和人群健康产生潜在危害, 近十多年来, 国际社会针对长链PFAS开展了管控行动并已取得进展. 2009和2019年联合国环境规划署分别将全氟辛磺酸(PFOS)及其盐类和相关化合物、全氟辛酸(PFOA)及其盐类和相关化合物列入《斯德哥尔摩公约》持久性有机污染物名单中, 除特定豁免和可接受用途的生产、流通和使用外, 要求减少并最终禁止使用[20]. 2023年, 美国国家环境保护局(EPA)宣布针对6种PFAS(PFOS、PFOA、全氟己烷磺酸(PFHxS)、全氟壬酸(PFNA)、六氟氧化丙烯二聚酸(GenX)和全氟丁烷磺酸(PFBS))拟制定国家初级饮用水法规标准[21]. 我国于同年4月1日起正式实施的《生活饮用水卫生标准(GB 5749-2022, 详情可参见 http://dghb.dg.gov.cn/attachment/0/168/168129/3983117.pdf)》也首次明确规定了生活饮用水中PFOA、PFOS的浓度限值. 由于含氟化合物的不可或缺性, 全球氟化工企业提出了多种替代策略, 并已开发众多替代品应用于工业生产中. 这些替代策略包括: (1) 短链替代长链: 使用碳链长度为4和6的全氟丁酸(PFBA)和全氟己酸(PFHxA)替代PFOA[22,23], 碳链长度为4的PFBS替代PFOS[24], 或者使用短链全多氟前体物, 如6:2氟调聚磺酰胺烷基甜菜碱[25]; (2) 多氟替代全氟: 分子中插入碳氢键或引入其他功能基团, 以降低全氟链段的长度, 如6:2氟调聚磺酸(6:2 FTSA)等[23]; (3) 插入氧原子, 减少含氟链段"有效长度": 如全氟及多氟聚醚羧酸(PFECA)和全氟及多氟聚醚磺酸(PFESA)等氧杂型替代品[26](部分醚羧酸的结构及名称见图1).

鉴于长链PFAS的环境持久性及新型替代品的广泛使用, 我国PFAS污染面临传统及新型PFAS共存, 并不

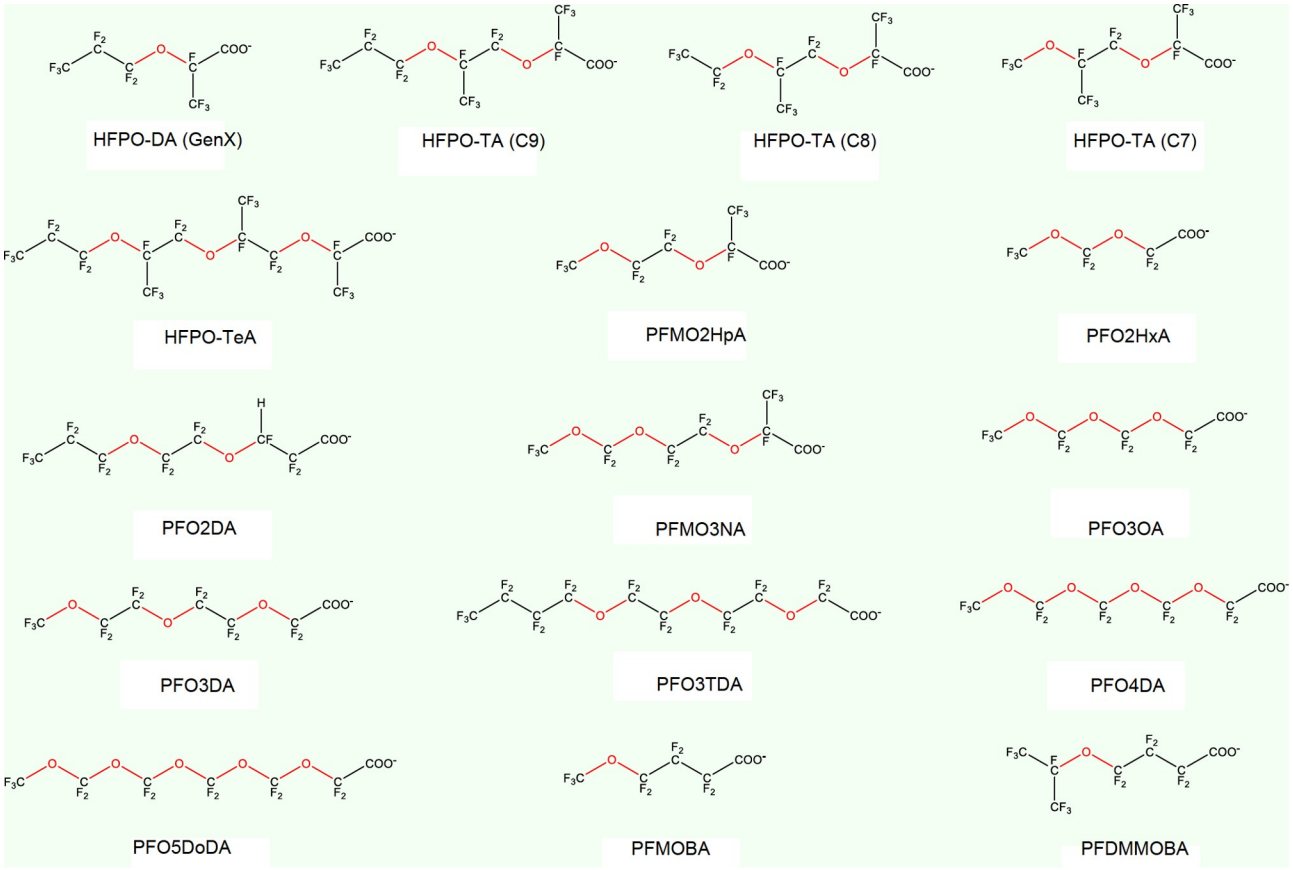

图 1 (网络版彩色)部分典型PFECA结构
Figure 1 (Color online) Structures of several representative PFECA

断迭代和演替的过程. 本文概述了新型全氟及多氟聚醚羧酸的识别、环境行为、生物累积、人群暴露水平及毒性效应, 围绕目前新型PFECA存在的问题及未来的研究方向进行了讨论和展望, 以期为PFAS替代品的环境污染及风险评估提供参考, 为我国开展PFAS的管控和削减行动提供支撑.

1 基于非靶向分析识别环境介质中的新型PFECA

PFAS的非靶向分析主要基于高分辨质谱(HRMS)获得的精确质荷比、二级谱图、同位素模式和碎片离子, 结合不同筛选/过滤手段, 或直接与PFAS数据库进行比对, 从而识别未知PFAS. 近年来, 利用HRMS技术, 结合系统的数据挖掘工作流, 研究人员已在各种复杂环境介质, 如工业废水[27~30]、自然水体[31~34]、大气颗粒物[35,36]、土壤沉积物[37]等中发现大量包括PFECA在内的各种新型PFAS. 但相关研究尚在起步阶段, 目前仅有11篇报道. 根据高分辨筛查结果的丰富度将其划分为5个置信水平(Level 1~5)[38], 以使未知PFAS的筛查和识别结果更具可比性. 通过PFAS同源物分析进行非靶标筛查, Yu等人[35]在大气样品中共发现117种PFAS同系物, 其中置信水平高于3的PFECA共13种, 全部为氯代全氟聚醚羧酸盐(Cl-PFECA). Jacob等人[30]在电子厂废水中识别出不饱和单醚PFECA、多氟单醚二羧酸/三羧酸等多种新型PFECA. McCord等人[32]在美国新泽西州西南部水样中发现了一系列Cl-PFECA和其他PFAS的存在. 随后Evich等人[37]也在该州土壤样品中识别出Cl-PFECA同系物, 并初步发现多种同源物的疑似转化产物包括H-PFPECAs、epox-PFPECAs和diOH-PFPECAs等. 此外, 围绕江苏常熟氟化学工厂周边区域, Yao等人[31]在环境介质中鉴定出了14类87种PFAS, 包括30余种主链上具有不同修饰的PFECA(例如, 支链甲基、氢取代和不饱和双键), 其中12种为首次报道. 目前在环境介质中已识别出的PFECA, 见表S1.

2 新型PFECA的环境行为及人体暴露特征

近年来, 研究人员在世界各地的环境介质中检出了多种新型PFECA, 包括水体、大气、土壤及沉积物等; 与此同时, 在野生动物和人体组织样本中也发现了这类物质的存在. 新型PFECA暴露正愈发成为一个全球性问题, 对生态环境和人体健康构成极大的潜在威胁.

2.1 水体

新型PFECA已在全球各地的水体中广泛检出, 以4,8-二氧杂-3*H*-全氟壬酸铵(ADONA)、六氟环氧丙烷(HFPO)同系物和全氟-2-甲氧基乙酸(PFMOAA)等为主. 2008 年, 在德国埃尔茨河一家氟化工厂的废水排放下游发现ADONA, 其浓度范围为320~6200 ng/L[39]. Heydebreck等人[40]于2015年首次报道了六氟环氧丙烷二聚体(HFPO-DA)在莱茵河及我国小清河水体中的存在. 此外, Joerss等人[41]在北极的海水中也检测到HFPO-DA, 其平均浓度为 0.03 ng/L, 暗示HFPO-DA具有与PFOA一致的长距离迁移性. Gebbink等人[42]在荷兰某氟化工厂下游河水中检测到HFPO-DA浓度高达812 ng/L, 周边城市饮用水中也普遍检出HFPO-DA (0.25~11 ng/L). 2017年, Pan等人[17]合成了C9-六氟环氧丙烷三聚体(C9-HFPO-TA)标准品, 并在我国小清河河水中首次检测出C9-HFPO-TA, 其在氟化学工厂下游水体中的浓度高达到 68.5 μg/L, 仅次于PFOA. 在此基础上, 进一步研究了中国、美国、英国、瑞典、德国、荷兰、韩国共7个国家主要河流或湖泊表层水样, 发现HFPO-DA、C9-HFPO-TA和ADONA 3种PFECA都有检出, 其中HFPO-DA在全部水样中的检出率达96%, 各水体中平均浓度范围为0.7 ng/L(长江)~14 ng/L(太湖). C9-HFPO-TA检出率为83%, 平均浓度范围为0.1 ng/L(泰晤士河)~5 ng/L(太湖)[14]. ADONA仅在莱茵河中检出. 此外, Sun等人[19]在美国开普菲尔河氟化学工厂下游自来水厂原水中检测到HFPO-DA的浓度高达631 ng/L, 同时还检测到PFMOAA、全氟-3,5-二氧基己酸(PFO2HxA)、全氟-3,5,7-三氧基辛酸(PFO3OA)和全氟-3,5,7,9-四氧基癸酸(PFO4DA)等新型PFECA, 但由于缺乏标准品, 未能精确定量, 但根据其峰面积可推测出浓度或高于HFPO-DA. Yao等人[31]通过合成相应标准品, 在我国常熟氟化学工业园厂区精准识别并定量了C7-HFPO-TA、C8-HFPO-TA、C9-HFPO-TA、PFMOAA、PFO2HxA、PFO3OA等新型PFECA, 其中C7-HFPO-TA浓度在厂区地表水、望虞河和太湖水体的中位数浓度分别为670、23和5.6 ng/L, 而在厂区污水处理厂出水浓度高达447000 ng/L. 同时, Yao等人[31]比较了2016~2021年间太湖水体中PFECA的水平, 发现以HFPO同系物、PFMOAA等为代表的PFECA浓度水平显著升高.

2.2 土壤及沉积物

PFECA较传统PFAS水溶性高，较难进入土壤和沉积物. 以HFPO-DA为例，其正辛醇-水分配系数的对数值($\log K_{ow}$)约为4.0[43]；相比之下，PFOA的$\log K_{ow}$值为4.81[44]. 现仅有2篇报道在氟化工厂周边土壤和沉积物中有所检出. Galloway等人[45]在美国西弗吉尼亚州帕克斯堡的一家氟聚物工厂周边土壤和底泥中检出HFPO-DA. Sun等人[33]也在华北地区辽宁省细河(阜新段)、山东省小清河(淄博段)和江苏省长江(常熟段)表层沉积物中检出较高浓度的HFPO-DA(均值浓度分别为22.2、12.9和2.95 ng/g)，且HFPO-DA是沉积物中PFAS的主要组成之一.

2.3 大气

研究表明 ADONA 可通过工厂废气释放至空气中，随后沉降至工厂周边表层土壤，其沉降速率约为684 ng/(m^2 d)[46]. 2018年，科慕公司向北卡莱罗纳州环境质量部报告 HFPO-DA 向大气中的排放量大约为2241 磅/年[47]，在北卡罗来纳州收集的雨水样品中发现HFPO-DA 的最高浓度约为 0.810 μg/L[48]. 由于PFECA具有较强电离能力(以HFPO-DA为例，20°C下pK_a为2.84[49])，在环境条件下多以电离态存在，可通过气溶胶进入气相迁移. PFECA可以在气相中迁移，也可以与颗粒物结合，并在释放或分配到空气中时与颗粒物一起迁移. 释放到空气中或者从水中挥发到空气中的PFECA，其化学性质是稳定的，可以在空气中发生长距离迁移. 空气中 PFECA 的去除主要是通过水滴清除和附着在微粒上，然后沉淀和沉降[50].

2.4 生物体和人群分布

与PFOA类似，PFECA也可在生物体中累积，仅有8篇文章报道了其在植物、淡水鱼类、海洋生物及蛙类中的浓度分布. Brandsma等人[51]在荷兰一个氟化学工厂附近的青草和树叶中检测出HFPO-DA，其浓度分别为1~27 ng/g(湿重)和4.3~86 ng/g(湿重). 德国巴伐利亚州立环境署[52,53]在德国代根多夫州的草中检测到ADONA浓度约为0.06~0.16 ng/g，在我国天津地区的刺槐中也检测到ADONA(0.209 ng/g)[54]. Guillette等人[55]在美国开普菲尔河鲈鱼血清中检测到HFPO-DA，其平均浓度为1.9 ng/mL. 近年来，在奥廷格森林鹿、海洋哺乳类生物的肝脏中也检测到一定浓度的ADONA[52,53,56]. 我们在山东小清河水样、野生鱼类血清中均检测到C9-HFPO-TA，鲤鱼血清中C9-HFPO-TA浓度仅次于PFOA，中位数浓度可高达1.5 μg/mL[17]. C9-HFPO-TA在鲤鱼和黑斑蛙体内的生物富集系数(BCF)高于PFOA，暗示其具有更强蓄积性，且C9-HFPO-TA比PFOA更易于在肝脏和皮肤中累积. Li等人[57]研究了山东省小清河——莱州湾新型PFAS的生物放大效应，发现全氟-3,5,7,9,11-五氧基十二烷酸(PFO5DoDA)、C9-HFPO-TA、六氟环氧丙烷四聚体(HFPO-TeA)等多种全氟醚羧酸的食物网放大系数(TMF)高达2.7~5.6，而被认为具有高蓄积性的传统PFOS的TMF仅为1.6，暗示这些新型PFECA对高营养级海洋生物或具有更大风险.

除野生动植物外，人体中也有 PFECA检出，但受限于部分PFECA标准品难以获得，目前仅有7篇相关报道. 2017年，杜邦公司报道其员工血浆中的 HFPO-DA 的浓度为 0.001~0.169 μg/mL[58]. 2013~2014年美国健康与营养检查调查(NHANES)12岁及以上参与者的2682份存档尿样中，1.2%的样品可检出HFPO-DA，其浓度在0.07~0.3 μg/L之间[59]. Fromme等人[60,61]分析了2009~2016年间居住在德国南部的献血者中收集的396份血浆样本，约6.5%的样本中检测到高于定量限(LOQ > 0.2 μg/L)的ADONA，最高浓度为14.4 μg/L. 最近，Hogue等人[12]在开普菲尔河周边居民血液中检测出PFO4DA(中位数浓度: 2 ng/mL，检出率: 98%)和PFO5DoDA(浓度 < 0.5 ng/mL，检出率: 98%). 本课题组在人群血清[62]、母乳、尿液[63]等样品中检出多种PFECA(表1)，血清样本采自氟化工厂周边居民，母乳、尿液和脐带血样本涵盖我国多个城市的正常母婴群体. 其中，氟化工园区周边人群血清中HFPO-TA的检出率>97.9%，中位数浓度为2.93 ng/mL，仅次于PFOA、PFOS和6:2氯代多氟聚醚磺酸(F-53B)成为当地居民血清中主要PFAS之一. 新型PFECA在环境、生物体和人体中分布水平的广泛检出(图2)表明其可能已造成潜在健康风险.

3 新型PFECA的毒性效应

结构类似的化合物往往表现出相似的毒性效应，PFECA可能表现出与PFOA类似的毒性效应，本文总结了已有研究中报道的PFECA毒性效应和相关机制(图3，表S2).

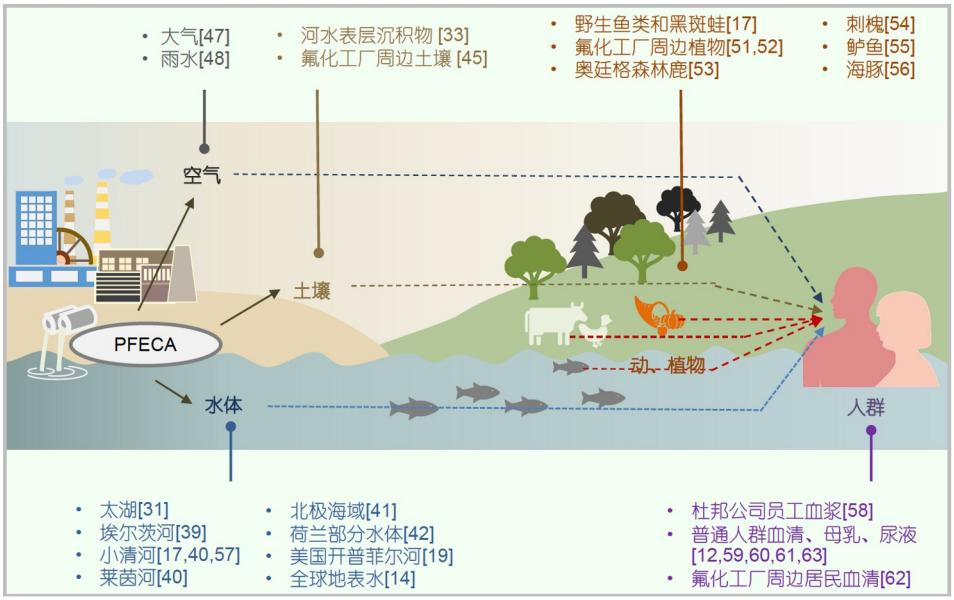

图 2 (网络版彩色)在环境、生物体及人体中检出新型PFECA的相关研究
Figure 2 (Color online) Selected studies on the detection of novel PFECA in environment, organism and human body

表 1 新型PFECA在各人体介质中报道的浓度水平[a)]
Table 1 Concentration of novel PFECA reported in different human samples

PFECA	血清(n = 977, ng/mL)	母乳(n = 1151, ng/L)	尿液(n = 80, ng/mL)	脐带血(n = 80, ng/mL)
PFMOAA	12.71 ± 20.68 (100)	4.816 ± 75.34(95.5)	30.88 ± 380.2(100)	171.4 ± 934.1(98.8)
PMPA	N.A.	N.D.	N.D.	N.D.
PF4OPeA	0.007 ± 0.024(17.1)	N.D.	N.D.	N.D.
PF5OHxA	N.D.	N.D.	N.D.	N.D.
HFPO-DA	0.028 ± 0.032(8.4)	3.056 ± 10.09(8.5)	1.627 ± 5.511(20.0)	25.75 ± 6.003(2.5)
PFBOPrA	N.D.	N.D.	N.D.	N.D.
PFO2HxA	0.033 ± 0.509(70.3)	0.733 ± 7.887(18.1)	0.851 ± 7.787(16.3)	7.157 ± 59.33(17.5)
PFO2HpA	N.D.	N.D.	N.D.	N.D.
PFO2OA	N.A.	N.A.	N.A.	N.A.
C7-HFPO-TA	N.A.	N.A.	N.A.	N.A.
C8-HFPO-TA	N.A.	N.A.	N.A.	N.A.
C9-HFPO-TA	1.805 ± 18.18(99.2)	1.783 ± 22.52(18.4)	0.955 ± 3.280(31.3)	149.2 ± 836.2(83.8)
PFO3OA	0.039 ± 0.261(29.6)	1.275 ± 34.27(42.7)	0.777 ± 4.335(42.5)	32.04 ± 145.3(77.5)
PFO3DA	N.A.	N.A.	N.A.	N.A.
PFO4DA	0.138 ± 0.325(95.9)	1.763 ± 11.03(29.8)	N.D.	73.05 ± 291.1(92.5)
PFO5DoDA	0.976 ± 2.76(100)	2.380 ± 9.002(71.2)	N.D.	154.4 ± 264.2(98.8)
3:2 H-PFECA	N.A.	N.A.	N.A.	N.A.

a) N.A., not available, 表示未获得相关数据; N.D., not detected, 表示未检出

3.1 新型PFECA对啮齿类毒性效应及潜在机制

肝脏毒性是PFOA具有代表性的毒性效应之一, PFOA暴露后, 啮齿类动物及非人类灵长类动物肝脏出现肝细胞肿大、脂质累积及急性肝损伤等现象. 28 d亚急性暴露实验发现HFPO-DA、HFPO-TA和HFPO-TeA

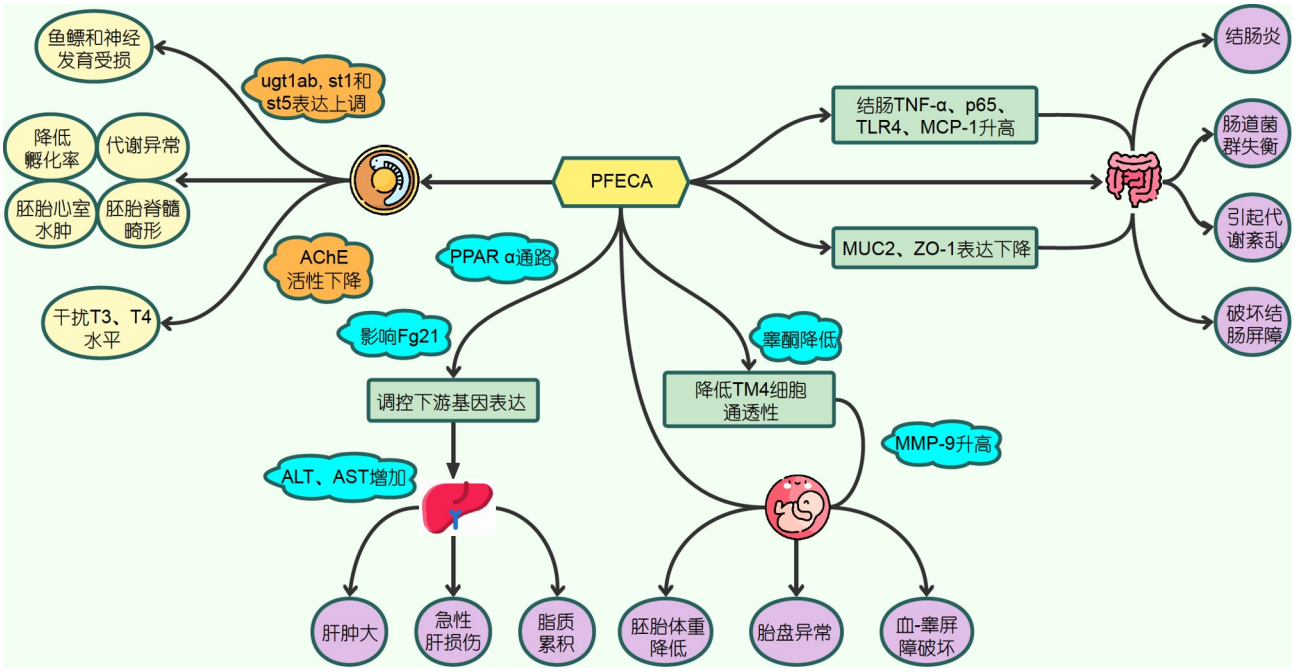

图 3 (网络版彩色)新型PFECA对鼠和斑马鱼的毒性效应和相关机制
Figure 3 (Color online) Toxicity and related mechanisms of novel PFECA on mice/rats and zebra fish

均可引起小鼠肝脏肿大，肝脏损伤指标如谷丙转氨酶(ALT)、谷草转氨酶(AST)等显著增加，血清及肝脏脂质水平改变[64~67]. 在啮齿类动物中过氧化物酶体增殖物激活受体α(PPARα)通路是PFOA发挥毒性效应的最主要通路，PFECA同样通过激活PPAR通路，调控下游代谢相关基因表达[66,67]. 此外，本课题组[67]前期研究发现相同暴露浓度下，C9-HFPO-TA肝脏毒性显著强于PFOA. C9-HFPO-TA暴露导致化学品致癌通路和/或肿瘤生成相关基因/蛋白发生显著变化，暗示该化合物或具有致癌潜能[66]. 通过长期慢性暴露实验，PFO4DA和PFO5DoDA可通过影响成纤维生长因子21(*Fgf21*)等关键调控因子表达水平，抑制肝脏中的应激信号通路，干扰葡萄糖和脂质代谢[68]；亦可在激活PPAR同时，抑制糖皮质激素受体(GR)活性，从而改变肝脏代谢谱[69]. 本课题组[70]还比较了相同暴露浓度下全氟-2-甲基-3,6-二氧基庚酸(PFMO2HpA)、PFO3OA、全氟-2-甲基-3,6,8-三氧基壬酸(PFMO3NA)和PFO4DA等PFECA与PFOA的毒性差异，发现这些PFAS可引起小鼠肝肿大，血清ALT、AST升高，甘油三酯(TG)和总胆固醇(TCH)降低，其毒性大小为: PFMO3NA > PFOA > HFPO-DA > PFO4DA/PFMO2HpA > PFO3OA.

除肝脏毒性外，PFECA暴露也可影响生殖. Conley等人[71]发现SD大鼠妊娠期暴露 HFPO-DA会导致母体肝重增加，血清甲状腺素和脂质水平降低，子代中雌性个体体重降低，雄性个体的生殖器官重量降低. Blake等人[72,73]在CD-1小鼠中得到相似的结论，即HFPO-DA暴露导致妊娠体重增加，胚胎体重降低，同时会导致母体肝肿大以及病变，胎盘发生异常，这与PFOA产生的毒理学效应相似. 此外，HFPO-DA、C9-HFPO-TA、HFPO-TeA暴露导致小鼠血清中睾酮水平降低，同时可通过降低TM4细胞的通透性，诱导基质金属蛋白酶-9(MMP-9)表达水平升高，激活p38丝裂原活化蛋白激酶(p38 MAPK)通路，从而控制occludin蛋白的降解，破坏血睾屏障(BTB)[74].

此外，有两项研究报道了PFECA对小鼠的肠毒性. Xie等人[75]发现HFPO-DA暴露可导致小鼠结肠炎症和结肠屏障功能障碍，盲肠菌群多样性发生变化，其可能的机制是: HFPO-DA暴露导致血清肿瘤坏死因子-α(TNF-α)水平升高，结肠的TNF-α、转录因子65(p65)、Toll样受体4(TLR4)、单核细胞趋化蛋白1(MCP-1) mRNA表达水平升高，进而引发炎症；同时结肠黏液糖蛋白2(MUC2)和紧密连接蛋白1(ZO-1)mRNA表达水平和对应蛋白水平下降，导致屏障功能障碍. Hu等人[76]则通过暴露C9-HFPO-TA发现，C9-HFPO-TA可造成肠道

菌群多样性失衡, 各菌群相对丰度发生变化, 引起糖脂代谢如不饱和脂肪酸合成、脂肪酸代谢、乙醛酸和二羧酸代谢和半乳糖代谢等紊乱.

3.2 新型PFECA对斑马鱼毒性效应及潜在机制

以斑马鱼为模型, 研究了PFECA的发育毒性、肝脏毒性、心脏毒性和甲状腺干扰效应等, 目前有6篇相关研究报道. Wang等人[77]比较了PFO3OA、PFO4DA、PFO5DoDA以及PFOA的发育毒性, 发现PFOA和PFECA亚急性暴露能够引起斑马鱼孵化率, 心率和畸形率显著变化, 其中鱼鳔未充气是最明显的畸形指标. 暴露120 h后将各化合物根据半数效应浓度(EC_{50})值进行毒性排序, 依次是PFO5DoDA(22.9±0.88 mg/L) > PFO4DA(117.1±13.3 mg/L) > PFOA(251.5±24.2 mg/L) >PFO3OA(1227.4±66.80 mg/L). PFOA和PFECA亚急性暴露干扰甲状腺水平稳态, 斑马鱼胚胎T3和T4的含量随着化合物浓度的升高显著降低. Gebreab等人[78]发现较高浓度的HFPO-DA、全氟-4-甲氧基丁酸(PFMOBA)、全氟-5-氧杂-6-二甲基己酸(PFDMMOBA)、全氟-3,6,9-三氧基癸酸(PFO3DA)、全氟-3,6,9-三氧基十三烷酸(PFO3TDA)、全氟-3,6-二氧基癸酸(PFO2DA)等均可造成急性胚胎毒性、发育受损和运动行为改变, 同时引起碳水化合物、脂质和氨基酸代谢障碍等各种代谢综合征. 此外, 研究发现HFPO-DA可抑制三磷酸腺苷酶和钙离子转运、线粒体相关功能调控基因和肿瘤/细胞增殖相关基因的表达[79], 并引起斑马鱼胚胎心率增加、心室水肿、脊柱畸形和水肿[80]. HFPO-TA暴露斑马鱼胚胎后, 斑马鱼胚胎肝内胆管发育异常, 肝脏胆汁酸代谢紊乱[81].

PFECA毒性机制研究表明[77], 与PFOA一致, 新型PFECA暴露可导致*ugt1ab*, *st1st5*表达上调, 从而增加甲状腺激素的糖基化和磺基化水平, 促进甲状腺激素的降解从而使斑马鱼体内甲状腺激素水平降低. 外源添加T3和T4可降低鱼鳔未充气的畸形率, 表明PFECA通过干扰甲状腺激素水平稳态, 影响斑马鱼鱼鳔的发育, 最终影响其生存. Gong等人[80]研究发现, HFPO-DA暴露可导致视觉反应相关基因表达下调而心血管系统相关基因上调, 可能是其胚胎发育毒性的潜在原因. 此外, Wang等人[82]研究表明HFPO-DA可通过影响下丘脑-垂体-甲状腺(HPT)轴、脂质代谢和细胞凋亡有关基因的表达, 造成乙酰胆碱酯酶(AChE)活性下降, 导致神经发育紊乱.

4 PFECA与转运蛋白/核受体的相互作用

血清白蛋白和肝脏脂肪酸结合蛋白被认为是PFAS在生物体血清和肝脏中累积的关键蛋白. Delva-Wiley等人[83]基于人血清白蛋白(HSA)与脂肪酸和PFOS结合的晶体结构数据, 研究了GenX与HSA的相互作用, 发现GenX与HSA间存在4个结合位点, 各位点具有不同的结合亲和力, 但不会干扰HSA的二级结构. Sheng等人[84]通过体外表达纯化人肝脏型脂肪酸结合蛋白(hL-FABP)结合分子对接模拟实验, 比较了HFPO-DA、C9-HFPO-TA、HFPO-TeA和PFOA的蛋白结合能力, 结果表明HFPO-TeA与蛋白亲和力最高, C9-HFPO-TA次之, HFPO-DA与hL-FABP蛋白亲和力最低.

除上述两种转运蛋白外, 一些研究也围绕上述HFPO同系物与不同核受体的相互作用开展了相关实验. Evans等人[85]评估了HFPO-DA、PFMOAA及其他14种PFAS、3种内源性脂肪酸和3种药物与人/大鼠PPARα/γ配体结合结构域结合(LBD)活性, 结果表明HFPO-DA的PPARα活性略低于油酸和亚油酸, 强于PFOA、PFOS等传统PFAS. Li等人[86]比较了PFOA、HFPO-DA和C9-HFPO-TA与hPPARγLBD区亲和力及PPARγ信号通路的激动活性, 发现C9-HFPO-TA与蛋白的结合亲和力是PFOA的4.8~7.5倍, 而HFPO-DA以及PFOA与蛋白的结合亲和力较弱, 三种PFAS对PPARγ信号通路的激动活性顺序为C9-HFPO-TA > PFOA > HFPO-DA. 此外, Xin等人[87]发现HFPO同源物可能比PFOA具有更高的雌激素作用. C9-HFPO-TA和HFPO-TeA对雌激素受体配体结合结构域(ER-LBD)的结合亲和力均高于PFOA, 而HFPO-DA的结合亲和力弱于PFOA. PFOA对ERs的信号通路表现出激活效应, C9-HFPO-TA和HFPO-TeA则表现出拮抗活性.

5 问题与展望

结构类似的化合物往往具有类似的环境行为及生物效应, 一个“有毒”化合物被另一个结构类似的化合物替代, 往往并不能真正解决毒性危害问题, 反而可能会陷入“化学品污染→替代→再污染”循环往复的怪圈. 因此, 在替代品的研发过程中, 除了充分考虑替代品的功能外, 需要充分阐明替代品结构与环境行为和毒性之间的关系, 从“源头”上探讨含氟替代品对环境和人类健康可能的不利影响, 根据系统性危害评估的结果指导化学合成, 使合成的替代品具有功能优

异、低生物蓄积性和低毒性等特性，有效预防和控制因毒害化合物的生产和产品带来的环境污染. 因此，针对替代品合成的问题，需要环境化学、生态毒理和有机氟化学科研工作者密切互动，通过环境化学和生态毒理学的交叉融合，指导开展全氟及多氟烷基物质替代品的设计和合成工作，摒弃对环境危害的过度结构修饰. 目前新型PFECA的研究和应用面临的主要问题包括：(1) 部分替代品结构、物理化学性质等信息不明确. 由于知识产权保护等原因，部分公司对研制的新型PFECA相关产品信息并不公开，为后续研究人员的化学分析、毒理学研究等工作带来挑战. (2) 缺少标准品，难以精确定量. 通过峰面积进行半定量，往往与真实值尚存在较大误差. (3) 缺乏精确、灵敏的定量分析方法. PFECA因含有醚氧原子，热稳定性差，在LC-MS/MS检测过程中存在源内裂解现象，难以获得稳定的$[M-H]^-$信号，导致灵敏度差. (4) 背景污染高. 液相色谱管路、仪器、耗材中广泛存在此类物质，致使仪器基线和方法空白升高，灵敏度下降. (5) 现存替代品的环境行为和毒性效应尚不明朗，其与替代品本身结构之间的联系有待探究. (6) 部分PFAS替代品仍具有较高生物蓄积性和毒性效应. 已有的数据表明，HFPO-TA等的生物蓄积性及毒性效应较传统PFOA更强.

有关全氟及多氟烷基物质及其新型替代品，今后应开展如下工作：(1) 鼓励公司公开替代品的信息，如替代品结构、性质、产量等；(2) 建立此类污染物精确、灵敏的定量分析方法；(3) 鉴定环境中未知结构的PFAS替代品，研究其在典型环境介质中的分布特征、生物蓄积性等环境行为和毒性效应；(4) 通过计算毒理学手段，特别是人工智能和机器学习算法等，构建替代品结构与毒性之间关系；(5) 开展低剂量、长期毒性和复合毒性研究，整合多种组学，从分子、基因等水平研究其毒性机制，通过系统性研究为研发“低持久、低毒、低蓄积性”的新型绿色PFAS替代品提供理论基础和技术支撑. (6) 开发更高效处理和降解环境中PFAS及其新型替代品的工艺，如膜技术[88]、吸附和离子交换[89]、电化学高级氧化[90,91]、高级还原[92]、光催化[93]、微生物降解[94]等. (7) 建立健全PFAS及新型替代品的相关政策法规和管控策略，完善市场监管体系，为绿色、合理使用PFAS相关化学品提供政策保障.

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补充材料

表S1 文献中识别的新型PFECA
表S2 新型PFECA毒性效应和相关机制的研究结果汇总

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Summary for “新型全氟及多氟聚醚羧酸识别、分布特征及毒理效应研究进展”

Recognition, distribution, and toxicities of novel per- and polyfluoropolyether carboxylic acids

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Per- and polyfluoroalkyl substances (PFAS) possess distinct properties, such as hydrophobicity, oleophobicity, and thermal and chemical stability, resulting in their wide application in various industrial processes, including electroplating, fire protection, and textile, paper, and leather production. However, due to their propensity for high bioaccumulation, long-distance transport, resistance to degradation, and potential adverse effects on animal and human health, certain PFAS, including “legacy” perfluorooctanoic acid (PFOA), were listed in Annex A of the Stockholm Convention in 2019, leading to a global ban on their production and usage. Consequently, per- and poly-fluoropolyether carboxylic acids (PFECA), containing ether oxygen bonds in their structure, have emerged as processing-additive substitutes for PFOA in different industries. Recently, with the increasing concern, more and more PFECA have been identified and detected in various environmental matrix and human samples. Epidemiological research and toxicity experiments have also found that some PFECA have health hazards comparable to or even stronger than PFOA.

In the present study, we focus on the classification, environmental impacts, and toxic hazards associated with PFECA and summarize recent research regarding non-targeted identification, environmental behavior and fate, biological/human exposure levels, toxic effects, and related molecular mechanisms. The overall aim of this review is to provide a valuable reference for environmental pollution research and biological risk assessment of PFAS alternatives, thereby supporting the regulation and reduction of PFAS alternatives in China.

In terms of PFECA recognition, with the rapid development of non-targeted and targeted screening techniques, researchers have identified a series of PFECA with feature structure in various environmental matrix, such as unsaturated PFECA, chlorinated PFECA and homologues of hexafluoropropylene oxide trimer acid (HFPO-TA). However, non-targeted and targeted screening research is still in its infancy, with only 11 reports identifying dozens of PFECA, more and more novel PFECA will definitely be recognized in the future.

In terms of quantitative detection, PFECA has been detected in various environmental matrix (including surface water, soil, atmosphere), organisms (including plants, fish and frogs) and even human samples (serum, urine and milk). Among them, there are many reports on water bodies and population samples. Among the existing reports, the PFECA levels in water and human samples accounts for a relatively large proportion. It is worth noting that the detection rate of HFPO-TA homologues in the serum of residents living around fluoride factories exceeds 90%, and the concentration of HFPO-TA ranking the fourth among all the detected PFAS.

In terms of the toxic effects, it has been confirmed through several animal exposure experiments that PFECA, such as HFPO-TA, hexafluoropropylene oxide tetramer acids (HFPO-TeA) and perfluoro (3,5,7,9-tetraoxadecanoic) acid (PFO4DA), can cause liver damage, decreased sex hormone levels, metabolic disorders, and developmental abnormalities by interfering with PPAR pathways and metabolic pathways. In addition to *in vivo* experiments, we also noticed that researchers have carried out in-depth *in vitro* and *in sillico* studies on the interaction between PFECA and nuclear receptors or transporters in order to provide a possible explanation for the bioaccumulation and toxic effects of PFECA.

Our paper also discusses the challenges, potential risks, and future research directions concerning the application of PFECA. For example, in the development and application of green alternatives, several problems, including unclear information on their structure, physical and chemical properties, and immature quantitative analysis methods, should be addressed to reduce the potential environmental and health hazards caused by the new PFECA at the source. At the same time, developing efficient degradation methods in contaminant treatment is also one of the future research directions. It is also worth paying more attention to combine regulatory, scientific research, and market aspects to provide guarantees for the rational use of novel PFECA.

PFECA, non-target screening, environmental behavior, human exposure, toxicity

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