全氟/多氟烷基化合物的毒理学研究进展及新型替代物健康危害

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摘　要: 全氟/多氟烷基化合物(per- and polyfluoroalkyl substances, PFASs)因具有优良的理化特性, 在当前工业生产领域具有无可替代的地位, 在世界各地被广泛使用, 但由于其具有极强的生物蓄积性和环境持久性, 进入环境后不易降解, 会对人体健康造成不可忽视的伤害, 包括神经、免疫、内分泌、生殖发育、肝肾毒性, 因此受到世界各国的重视和严格的管控。传统 PFASs 的使用受限导致替代物被大量开发, 近几年在环境和生物体内检测到越来越多的新型替代物, 同时它们表现出比传统 PFASs 更强的生物毒性, 但目前依然缺乏对于 PFASs 替代物及前体的毒性研究和暴露评估数据。本文对近 5 年传统 PFASs 的毒理学研究结果进行综述, 并对几种检测频率较高的替代物及前体的人体接触水平及对健康的影响进行总结, 为 PFASs 新型替代物的进一步研究和监管措施提供科学依据。

关键词: 全氟/多氟烷基化合物; 新型替代物; 毒理学; 人群健康危害

Toxicological research progress of per- and polyfluoroalkyl substances and health hazards of novel alternatives

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ABSTRACT: The per- and polyfluoroalkyl substances **(**PFASs) with excellent physical and chemical properties, has the irreplaceable status in the field of the industrial production currently, and is widely used all around the world. Since it has strong bioaccumulation and persistence in the environment, it is not easy to degrade and can do considerable damage to human body health, including neurotoxicity, immunotoxicity, endocrine toxicity, reproductive and developmental toxicity and hepatorenal toxicity. Therefore, it is highly valued and strictly controlled by countries all over the world. The increasingly stringent restrictions on legacy PFASs have led to the compensatory use of new fluorinated replacements. However, in recent years more and more new alternatives are detected in the environment

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and the organism, and they showed stronger biological toxicity than legacy PFASs, but still lack of toxicity studies and exposure assessment data for novel PFASs and precursors. This paper reviewed the toxicological research results of traditional PFASs in the past 5 years, and summarized the human exposure levels and health effects of several substitutes and precursors with high detection frequency, which providing scientific basis for further research and regulatory measures of new PFASs substitutes.

KEY WORDS: per- and polyfluoroalkyl substances; novel alternatives; toxicology; human health hazards

0 引 言

全氟/多氟烷基化合物(per- and polyfluoroalkyl substances, PFASs)是全部或部分氟化、末端具有磺酸基或羧酸基的有机分子[1], 由于氟的强电负性和较小的原子尺寸, 与碳氢化合物相比, 全氟烷基部分($C_nF2_{n+1}^-$)赋予分子更为优良的化学稳定性、热稳定性、疏水、疏油和高表面活性[2], 被广泛应用于消费产品, 如一次性食品包装、炊具、户外用品、家具和地毯[3]。全氟烷基羧酸(perfluoroalkyl carboxylic acids, PFCAs)和全氟烷基磺酸(perfluoroalkane sulfonic acids, PFSAs)是家族中最常见和被研究最多的组分[4]。由于具有远距离迁移能力和食物链放大效应, PFASs 已经存在全球范围的环境污染[5]。PFASs 可通过灰尘吸入、膳食摄入等途径导致人体暴露并在体内蓄积[6−7]。与其他大多数持久性有机污染物相比, 它们不倾向于在脂肪组织中积累, 而是与血清白蛋白和其他胞浆蛋白结合, 主要在血液、肝脏、肾脏和胆汁中积聚[8−9], 因此血液样本是最为常见的 PFASs 的人体暴露监测样本[10]。另外母乳[11]、精浆[12]、脐带血[13]和肝脏[14]中也有广泛检出。人体对 PFASs 的主要暴露途径是摄入受污染的食物, 尤其是动物性食品[7], 在肉类、海鲜和乳制品中多见[15−18]。毒理学和流行病学研究表明, PFASs 可对多个器官产生直接或间接的毒性作用[19−20], 包括神经毒性[21]、生殖毒性[22]、代谢毒性[23]、发育毒性[24]、免疫毒性[25]、内分泌毒性[25]、肝毒性[26]和肾毒性[27]。

全氟辛酸(perfluorooctanoic acid, PFOA)和全氟辛烷磺酸(perfluorooctane sulfonic acid, PFOS)是环境、生物群和人体组织中检出率和浓度水平最高的两种全氟烷基化合物[28]。美国环境保护署(Environmental Protection Agency, EPA)对饮用水中 PFOS 和 PFOA 的健康建议限值为 70 ppt 或 70 ng/L。一项针对美国 25 家饮用水处理厂处理过的水的研究发现, 17 种 PFASs 的平均质量浓度为 19.5 ng/L, 最大质量浓度为 1.1 μg/L (1100 ng/L)[29]。在密歇根州一个主要都市区饮用水供水管道中, PFOA 和 PFOS 的平均质量浓度分别为 2.2 和 2.9 ng/L[30]。考虑到它们具有环境持久性、生物累积性和多种潜在毒性, PFOS 和 PFOA 先后于 2009 年和 2019 年被添加到《斯德哥尔摩公约》进行监管[31−32]。2022 年 6 月 10 日, 第 10 次缔约方会议对将全氟己烷磺酸(perfluorohexane sulfonic acid, PFHxS)及其相关化合物列入《斯德哥尔摩公约》附件 A 持久性有机物消除清单且不设任何豁免条件的提案进行审议, 目前还未正式发布决议[33]。传统长链 PFASs 的逐步淘汰导致替代物的大量使用, 包括作为 PFOS 替代物的氯化多氟烷基醚磺酸(chlorinated polyfluoroalkyl ether sulfonic acid, Cl-PFESAs, 商品名 F-53B), 以及 PFOA 的替代物 4,8-二氧杂-3-氢-全氟壬酸(dodecafluoro-3H-4,8-dioxanonanoate, ADONA)和六氟环氧丙烷二聚酸(hexafluoropropylene oxide dimer acid, HFPO-DA, 商品名 GenX), 然而这些新型替代物是否更为安全依然存在较大的争议。例如基于人体样品监测结果推测 F-53B 的人体生物半衰期高达 15.3 年, 远高于 PFOS[34]。近年来, 新型替代物在世界多个地方的空气[35]、大气[36]、水体[37]、灰尘[38]、沉积物[39]等各种环境介质以及生物体和人体样本中均被检测到, 并且在很多方面表现出超过传统 PFASs 的毒性[40−41], 这引起了人们广泛的关注。本文旨在对传统 PFASs 的毒理学研究进展进行总结, 并对近 5 年检测率较高的新型替代物在毒理学和人群健康危害方面的研究结果进行概括, 为今后对新型替代物的研究提供方向性指导和重要参考。

1 传统 PFASs 的生物毒性

1.1 PFASs 的神经毒性

PFOS 通过剂量依赖和时间依赖的方式显著影响日本三角涡虫基因表达[21], 并导致秀丽隐杆线虫超氧化物增多、神经元中线粒体减少以及行为异常, 而抗氧化剂可以降低线粒体氧化应激, 谷胱甘肽可改善多巴胺能神经变性和行为缺陷[42]。在一些研究中, PFOA、全氟壬酸(perfluoro-*n*-nonanoic acid, PFNA)、PFOS、全氟十二烷酸(perfluoro-*n*-dodecanoic acid, PFDoA)影响了斑马鱼游泳速度以及视觉运动反应[43−47], 它们更容易受惊吓且惊吓后爆发运动次数增加, 表明 PFASs 会增加焦虑[43,48]。在表达人类 $\alpha_1\beta_2\gamma_{2L}\gamma$-氨基丁酸 A 型受体($\gamma$-aminobutyric acid type A receptor, $GABA_AR_s$)的大鼠卵母细胞中, PFOS[最低观察到的效应浓度(lowest observed effect concentration, LOEC) 0.1 μmol/L]和 PFOA (LOEC 1 μmol/L)抑制 γ 氨基丁酸(γ-aminobutyric acid, GABA)诱发电流并充当非竞争性人类 $GABA_A$ 受体拮抗剂。暴露于 PFOS (LOEC, 100 μmol/L)后, 大鼠原代皮层培养物的神经元网络活动增加。此处报道的 PFASs 的

LOECs 处于或低于职业暴露人群血液水平中 PFASs 的浓度范围, 而 PFOS 的 LOEC 甚至低于普通人群血清和血浆中 PFASs 的水平, 这表明 PFASs 存在明显的神经毒性[49]。在意大利 PFASs 污染地区居民的大脑解剖样本中, 脑干区域聚集了大量多巴胺能神经元(dopaminergic neurons, DNs), 在通过分化人类诱导多能干细胞(human induced pluripotent stem cells, hiPSCs)获得的 DNs 模型中发现 PFOS 对神经系统的影响主要发生在神经多巴胺能分化最敏感的阶段[50]。

1.2　PFASs 的免疫毒性

PFASs 被证实对生物体具有免疫毒性, 但是动物实验中存在关联不一致的结论。PFASs 可减少淋巴细胞、粒细胞和三碘甲状腺氨酸(triiodothyronine, T3)的数量[26], 影响参与 T 细胞和 B 细胞功能的基因的转录水平[25], 经皮暴露会激活 α 型过氧化物酶体增殖物激活受体(peroxisome proliferators-activated receptor, PPAR)参与免疫应答[51]。但在一项研究中以 1.5 μg/(kg·d)剂量的 PFOS 暴露 4 周不会减轻小鼠体重或影响小鼠生存, 也不会抑制免疫细胞发育或引起抗原特异性免疫反应[52]。此外还发现 PFASs 介导的免疫调节功能会影响病原体与禽类宿主间的相互作用。PFOS 暴露 36 h 后, 鸡成纤维细胞免疫基因表达下降, 而感染禽疱疹病毒 2 型(gallid hepers virus 2, GaHV2)可以缓解这种抑制并使基因表达恢复到对照组水平[53]。

1.3　PFASs 的代谢毒性及肝毒性

细胞和动物实验中发现 PFASs 可扰乱细胞代谢并存在肝毒性。去绒毛斑马鱼胚胎暴露于 PFBS 后, 胚胎生长发育、能量稳态(脂质代谢平衡)和胰腺器官发育异常[54], 而胚胎期是 PFASs 影响代谢的易感窗口期, 这些早期暴露可对生命后期产生持久性影响[55]。使用超低、极低和低水平 PFASs 暴露剂量对受精后 0~5 d 的斑马鱼幼鱼进行处理, 在 F0、F1、F2 代中均观察到脂质通路被破坏[24]。将小鼠暴露于 PFASs 混合物, 观察到脂代谢发生改变(包括胆固醇和胆汁酸增加)、多种代谢途径被调节, 并伴有一些性别二态效应, 此外还发现小鼠肝损伤, 可能 PFASs 混合物通过破坏肠肝循环来介导胆固醇水平调节[56]。经真皮接触七氟丁酸(heptafluorobutyric acid, PFBA)可诱导小鼠肝毒性和 PPAR 靶基因的改变, 提示可能存在 PPAR 通路的作用[26]。将肝癌细胞株(human hepatoellular carcinomas, HepG2)细胞暴露于不同水平的 PFOA, 细胞周期基因和必需脂质代谢基因均受到显著影响[23]。另外, 在研究 PFOS 和 PFHxS 对饮食性肥胖小鼠模型血脂和肝脏蛋白质组的影响时发现, PFASs 可能通过诱导脂质代谢失调和氧化应激来增加饮食引起的代谢性和炎症性疾病的风险[57]。

1.4　PFASs 的内分泌干扰毒性

PFASs 作为一种持久性内分泌干扰物, 被证明对动物和人体存在内分泌干扰毒性。挪威斯瓦尔巴群岛海象的血浆中总甲状腺素(total thyroxine, TT4)浓度以及 TT4 与反三碘甲状腺原氨酸的比值随脂肪中 PFASs 浓度的增加而降低[25]。在老鼠模型中 PFOA 以剂量和时间依赖性的方式降低甲状腺细胞活力, 并改变了甲状腺细胞中的基因表达, 改变的基因表达似乎与 PFASs 和细胞的类型有关[58]。CONTI 等[59]发现 PFOS 对甲状腺细胞的碘积累具有急性和可逆性抑制作用, 甲状腺细胞内碘稳态的破坏可能是 PFOS 损害甲状腺健康的潜在机制。在一项体外人细胞系实验中, PFASs 浓度为 10 μmol/L 时观察到雌雄激素受体被激活及甾体分泌, 浓度低于 10 μmol/L 时, PFAS 对任何分子内分泌终点均无任何影响。由于一般人群血清中 PFASs 的浓度范围不超过 10 nmol/L, 根据此研究结果, 暴露在相同浓度下, PFASs 可能不会对人类的内分泌产生影响[60]。

1.5　PFASs 的生殖及发育毒性

PFASs 具有生殖毒性, 并会影响后代的生长发育。斑马鱼受精后胚胎中 PFOS 浓度随暴露浓度而显著增加[43–44]。PFOS 和 PFBS 可能会引起秀丽隐杆线虫活性氧水平升高导致生殖细胞凋亡, 并使部分抗氧化基因和促凋亡基因的表达发生显著变化[61]。将雌鼠暴露于不同水平的 PFOS 和 PFOA, 会影响幼鼠下丘脑-垂体-性腺(hypothalamic-pituitary-gonadal, HPG)轴的调节, 从而导致发情期提前, 并改变随后的生殖神经内分泌功能[22]。PFOA 可增强人绒毛膜滋养层细胞中 Notch 信号, 这可能是了解 PFASs 作用模式的关键, 因为该通路和许多与 PFASs 暴露相关的生理/毒理学症状密切相关[62]。在研究 PFASs 对体外胎盘滋养层的影响中发现, PFOA 和 PFOS 的细胞积累依赖于血清培养条件, PFOA、PFOS 改变了与增殖、合胞化和转运有关的几个编码蛋白的基因的表达。B 淋巴细胞瘤-2 基因(B-cell lymphoma-2, *bcl-2*), 是细胞凋亡研究中最受重视的癌基因之一, 在此研究中, 凋亡基因 BCL-2 相关细胞死亡激动剂(BCL-2 associated agonist of cell death, BAD)和 BCL-2 关联 X 蛋白(BCL-2 associated X protein, BAX)的表达变化最为明显。即使细胞对单个 PFASs 积累较低, 胎盘毒理学反应也可能出现[63]。PFASs 容易穿过胎盘, 胎儿处于发育的关键窗口期, 其生长发育很容易被干扰。HAIMBAUGH 等[24]研究 PFOS、PFOA 及其混合物对斑马鱼行为和非靶向基因表达的跨代影响, 他们使用超低、极低和低水平 PFASs 暴露剂量(7、70 和 700 ng/L PFOA; 24、240 和 2400 ng/L PFOS; 逐步混合物)对受精后 0~5 d 的斑马鱼进行处理, 观察幼鱼的死亡率、形态、行为和基因表达情况以及 F0、F1 代成年鱼的繁殖情况。结果显示 PFASs 水平不影响生存率, F1、F2 代均未发现形态学异常。但行为和基因表达失调是可遗传的, 即使在没有直接或间接接触 PFASs 的幼鱼中也是如此。

2 新型替代物的毒理学研究及健康危害

随着 PFOS 和 PFOA 的逐步淘汰, 越来越多的替代物被开发出来, 如作为 PFOS 的替代品的 Cl-PFESAs(商品名 F-53B)。F-53B 是一种复合混合物, 其主要成分是 6:2 氯化多氟醚磺酸(6:2 chlorinated polyfluorinated ether sulfonic acid, 6:2 Cl-PFESA), 仅在中国被用作电镀行业的抑雾剂。然而, 直到 2013 年, F-53B 的持久性、潜在毒性以及在环境中的存在情况被首次报道时才引起人们的广泛关注[64]。与传统 PFASs 相比, 有关新型替代物的信息较为缺乏, 但如今已有的研究表明, 环境中新型替代物主要有两种来源: 1)直接来源指 PFASs 在生产、使用、运输、处理等过程中直接排放进入环境; 2)间接来源指前体物质的降解及远距离迁移[65]。近年来, 新型替代物在世界多个地方的环境介质以及生物体和人体样本中均被检测到, 在相关工厂附近检出的浓度较高, 如在荷兰的一家氟化工厂下游检测到 GenX, 质量浓度高达 812 ng/L[66]。PAN 等[37]在中国、美国、英国、瑞典、德国、荷兰和韩国搜集到的地表水中均发现 HFPO-DA、六氟环氧三聚酸(hexafluoropropylene oxide trimer acids, HFPO-TA)。F-53B 主要存在于中国, 在地表水[67]、海水[68]、大气[69]、泥沙[70]和污水污泥[71]中均有检出。目前 F-53B 只在中国使用, 但在美国、德国、英国、荷兰和韩国的河流和湖泊中都普遍发现了 F-53B[37], 表明 PFASs 新型替代物已经成为了全球性污染物[72]。对几种来自北欧的顶级捕食者和可能被它们捕食的鱼类进行研究, 唯一检测到中国制造的 F-53B 是英国东盎格鲁地区的水獭样本(浓度为 3.3 ng/g 湿重)。在所有动物体中均检测到 3 种全氟烷基次膦酸(perfluoroalkyl phosphinic acids, PFPiA)(6:6 PFPiA、6:8 PFPiA 和 8:8 PFPiA)。由于水獭和海豹生活在淡水或海洋区域, 经常受到人类活动的影响, 它们比陆地捕食者秃鹰更容易受到 PFASs 和其他持久性有机污染物的污染[73]。新型替代物和传统 PFASs 相似, 具有组织特异性积累, 如 6:6 PFPiA 和 8:8 PFPiA 在鲤鱼血液中浓度最高, 在肌肉中浓度最低, 两种 PFPiAs 与血清中蛋白的结合力均高于肝脏中的蛋白[74]。PFOS 和氯化十八氟辛烷磺酸盐(chlorinated perfluorooctane sulfonate, Cl-PFOS)在虹鳟鱼组织中的生物蓄积能力(血液>肝脏>肾脏)和分布趋势相似。Cl-PFESAs 主要在肝脏和肾脏中吸收与代谢[75]。

2.1 毒理学研究

一些动物研究表明, 新型替代物具有器官毒性、代谢毒性和生殖毒性。ANNUNZIATO 等[76]首次证明了斑马鱼在受精后 5 d 时 PFHxA、PFHxS 和 6:2 氟调聚醇[2-perfluorohexylethanoic acid (6:2), 6:2 FTOH]的半致死浓度(lethal concentration 50%, LC_{50})。PFHxA 和 PFHxS 的 LC_{50} 值具有可比性; 然而, 6:2 FTOH 的急性毒性较小。此外, 在检测的最低浓度下(即 0.02 μmol/L), 基因表达发生改变, 这是本研究中最敏感的终点。暴露于 50 mg/kg 的全氟-4-甲氧基丁烷酸(perfluoro-4-methoxybutanioc acid, PFMOBA)可增加公鼠的相对肝脏重量, 使脾脏细胞发生变化, B 细胞和自然杀伤(natural killer, NK)细胞数量减少, 但在给药剂量下, 暴露没有改变 NK 细胞毒性或 T 细胞依赖性抗体反应[77]。在短期和长期毒性研究中对 HFPO-DA 的毒性进行评估, 结果表明, 肝脏是啮齿类动物经口腔接触 HFPO-DA 后毒性的主要靶点[78]。与其他长链 PFASs 类似, HFPO-DA 可以激活 PPAR-α 通路, 引起肝脏脂质代谢的改变[79]。妊娠期暴露 HFPO-DA 可增加母体胎盘异常率, 并上调子代 PPAR 信号通路相关基因的表达[79−80]。在细胞水平上, HFPO-DA 暴露可降低大鼠甲状腺细胞活力, 诱导遗传毒性, 降低大鼠甲状腺细胞系的增殖能力[81]。全氟(3,5,7-三氧杂辛酸)[perfluoro (3,5,7-trioxaoctanoic) acid, PFO3OA]、全氟(3,5,7,9-四氧杂十二烷酸)[perfluoro (3,5,7,9-tetraoxadecanoic) acid, PFO4DA]和全氟(3,5,7,9,11-五氧杂十二烷酸)[perfluoro (3,5,7,9, 11-pentaoxadodecanoic) acid, PFO5DoDA]属于全氟烷基醚羧酸(perfluoropolyether carboxylic acids, PFECAs), 也是 PFOA 的新型替代物。PFO4DA 可引起肝毒性, 表现为肝肿大和细胞核溶解, 但程度低于 PFOA[82], PFO5DoDA 比 PFO4DA 具有更强的肝毒性和更长的血清半衰期, 还会扰乱葡萄糖和脂质代谢[83]。对于碳链长度相同(即 C8)的 PFOS、Cl-PFOS 和 6:2 Cl-PFESA, 尽管它们取代基不同, 但都对脂代谢反应基因表现出相似的激活模式和破坏性。8:2 Cl-PFESA(即 C10)优先干扰脂肪酸分泌, 对过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors, PPARs)的拮抗作用明显高于其他化合物[84]。Cl-PFESAs 可能通过激活雌激素受体(estrogen receptor, ER)通路引起雌激素紊乱[85], 长期暴露于 Cl-PFESAs 会对鱼类造成持续的甲状腺激素干扰效应[86], 并且 Cl-PFESAs 可在亲代性腺中积累, 通过卵转移给后代, 在胚胎中出现较高的畸形发生率和较低的存活率[87]。在两栖动物黑斑蛙中, 6:2 Cl-PFESA 在雌蛙卵巢中的浓度占雌蛙全身 6:2 Cl-PFESA 浓度的 58.4%[41]。使用斑马鱼胚胎来比较各种 PFECAs 的发育毒性, 基于半最大效应浓度(half maximal effective concentrations, EC_{50})的毒性强弱为: PFO5DoDA>PFO4DA>PFOA>PFO3OA。PFECAs 与 PFOA 相似, 可造成 TH 代谢紊乱, 这会导致鱼鳔畸形。此外, 随着 PFECAs 主链中 OCF2 基团的数量增加, 鱼鳔畸形概率也增加, 表明主链中的原子数量在毒性中起着重要作用[40]。

2.2 人群健康危害

人类接触 F-53B 的途径尚不清楚, 但有研究报道了 F-53B 可通过食物[88−89]、饮用水[90]、室内空气和灰尘[6]使普通人轻易接触到它。特别的是, 母亲可以通过胎盘[91]和母乳[11]将 F-53B 传递给婴儿, 导致生命的早期暴露。

F-53B 在人体内有较高的蛋白结合亲和力和胎盘转移效率[92], 甚至可以穿过血脑屏障(cerebrospinal fluid barrier, CSF)渗透到脑脊液[93]。F-53B 在人体内的半衰期为 15.3 年, 是迄今为止人类体内生物持久性最强的 PFASs。对部分中国人的血液进行检测, F-53B 的浓度在 PFASs 中排名第 2~3 位[94–99]。

在受氟化工生产厂污染地区的居民可能存在较高浓度的新型替代物暴露。在北卡罗来纳州威尔明顿的居民(参与者年龄从 6 岁到 86 岁不等)中, 85%的参与者血清中检测到 PFO4DA 和 PFO5DoA, GenX 未超过方法检出限(2 ng/mL)[100]。中国山东一家氟化工厂附近居民血清样本中 PFECAs 的总浓度占参与者血清中总 PFASs 浓度的 13%, 检测率大于 95%的 PFECAs 有全氟-2-甲氧基乙酸(perfluoro-2-methoxyacetic acid, PFMOAA)、PFO4DA 和 PFO5DoDA(中位浓度分别为 12.91、0.142 和 0.987 ng/mL), 全氟烷基醚磺酸(perfluoroalkyl ether sulfonic acids, PFESAs)检出率大于 98.7%, 中位浓度为 0.097 ng/mL。男性血清中 PFMOAA、PFO5DoDA 和 6:2 Cl-PFESA 水平显著高于女性[101]。在生物监测方面, 尿液可作为一些短链和中链 PFASs 内暴露的有效测量指标, 而指甲和头发样本内暴露测量的有效性可能因 PFASs 和人群而异。在武汉和石家庄高暴露人群的指甲、头发和尿液中均检测到 C8 Cl-PFESA, 表明中国广泛存在这种污染物[102]。

新型替代物对人体具有生殖毒性、代谢毒性、内分泌毒性和器官毒性。健康女性卵泡液样品被检测出 6:2 Cl-PFESA 和 C8 PFECA, 4:4 C8 PFESA 和 Cl-PFESAs 的滤泡转移效率分别显著高于 PFOA 和 PFOS[103]。成年男性的性激素结合球蛋白(hormone-binding globulin, SHBG)水平与 PFNA、PFOS 和 6:2 Cl-PFESA 暴露有关[104]。北京脐带血血库从 1998 年到 2018 年每 5 年收集一次脐带血血浆样本, 血浆中 6:2 Cl-PFESA 在每个采样年的脐带血浆 PFASs 浓度排名第二或第三[13]。在 2016 年于中国河南省收集的 54 份胎盘样品中, 6:2 Cl-PFESA 的检测率为 100%, 平均湿重为 0.104 ng/g[91]。PFASs 替代物的胎盘转移率与链长密切相关并且可能比传统 PFASs 更容易穿过胎盘[105]。在中国广东省广州市, 一个出生队列由一家医院里从 2013 年 7 月至 10 月接受产前护理的 372 位母亲和她们的新生儿组成, 母亲血清中 PFOS 含量最高, 其次是 6:2 Cl-PFESA, 所有 PFASs 替代物浓度与低出生体重显著负相关, 母体血清中更高浓度的 6:2 Cl-PFESA 和 PFOS 也与更高的早产风险相关[94]。HFPO-DA 和 ADONA 也在中国北方沿海地区孕妇血清中被检测到[97]。另一项病例对照研究中发现, 暴露于 6:2 Cl-PFESA 和 HFPO-DA 与不明原因复发性自然流产(unexplained recurrent spontaneous abortion, URSA)风险增加显着相关[106]。母乳中也检测到较高浓度的 6:2 Cl-PFESA (28 pg/mL), C8~C10 PFCAs 和 6:2 Cl-PFESA 的浓度与婴儿身长增长率呈负相关[107]。血清中 6:2 Cl-PFESA 的浓度与人群代谢综合征(metabolic syndrome, MetS)患病率正相关[108]表明其代谢毒性不容忽视。6:2 Cl-PFESA 与血清 TC 和 LDL-C 呈正相关, 8:2 Cl-PFESA 暴露量与 HDL-C 呈负相关, 提示 Cl-PFESAs 是 2 型糖尿病的潜在致病因素[109–110]。PFO5DoDA 的水平与脂质参数、肝功能标志物和尿酸水平正相关[101]。此外, 在中国 C8 异构体健康项目(the isomer of C8 health project in China)招募者的血清中发现 6:2 PFESA 和 8:2 PFESA PFASs 浓度与乙型肝炎表面抗体(hepatitis B surface antibody, HBsAb)呈负相关。6:2 PFESA 与 HBsAb 血清阴性之间的关联似乎比 PFOS 更高, 表明新型替代物可能存在免疫毒性[111]。

3　结束语

PFASs 已成为全球性污染物, 在许多环境媒介和生物体中均发现这些物质的存在。由于 PFASs 具有环境持久性、生物蓄积性、毒性和远距离迁移性, 越来越多的 PFASs 被限制生产和使用, 导致替代物的大量出现。虽然现在还缺乏毒理学和流行病学资料, 但已有证据证明, 新型替代物与多种不良健康后果有关, 有些物质表现出比传统 PFASs 更强的毒性, 但其作用机制尚未明确, 一些潜在毒性也尚未发现, 这对人类健康风险评估构成重大挑战。人类暴露在 PFASs 的复杂混合物中, 然而目前获得的实验数据大多是通过单一物质接触得到的, 尤其是新型替代物, 这可能导致在预测总体风险时产生偏移。另外, 性别、基因等内在因素可能使 PFASs 对人体的影响存在差异, PFASs 与内源性激素及外界环境的相互作用也可能改变不良健康结果。因此, 需要进一步调查新型替代物对人类健康的影响以获取更多相关数据, 并严格管控 PFASs 的生产、使用、运输、处理等过程, 减少 PFASs 通过直接途径或间接途径进入环境。

参考文献

[1] LI PY, OYANG XH, ZHAO YL, *et al*. Occurrence of perfluorinated compounds in agricultural environment, vegetables, and fruits in regions influenced by a fluorine-chemical industrial park in China [J]. Chemosphere, 2019, 225: 659–667.

[2] DALY ER, CHAN BP, TALBOT EA, *et al*. Per- and polyfluoroalkyl substance (PFAS) exposure assessment in a community exposed to contaminated drinking water, New Hampshire, 2015 [J]. Int J Hyg Environ Health, 2018, 221(3): 569–577.

[3] SUNDERLAND EM, HU XDC, DASSUNCAO C, *et al*. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects [J]. J Expo Sci Environ Epidemiol, 2018, 29(2): 131–147.

[4] KATARZYNA SK , SURMA M, CIESLIK I. A review of perfluoroalkyl acids (PFAAs) in terms of sources, applications, human exposure, dietary intake, toxicity, legal regulation, and methods ofdetermination [J]. J Chem, 2019, 2019: 2717528.

[5] GIESY JP, KANNAN K. Perfluorochemical surfactants in the environment [J]. Environ Sci Technol, 2002, 36(7): 146A–152A.

[6] XU FP, CHEN D, LIU XT, *et al*. Emerging and legacy per- and polyfluoroalkyl substances in house dust from South China: Contamination status and human exposure assessment [J]. Environ Res, 2021, 192: 110243.

[7] LIU YF, LI Y, ZHAO NN, *et al*. Occurrence of perfluoroalkyl substances in animal-derived food in Beijing and risk assessment of residents' intake [J]. Environ Chem, 2021, 40(11): 3360–3367.

[8] JONES PD, HU WY, COEN W, *et al*. Binding of perfluorinated fatty acids to serum proteins [J]. Environl Toxicol Chem, 2003, 22(11): 2639–2649.

[9] PEREZ F, NADAL M, NAVARRO-ORTEGA A, *et al*. Accumulation of perfluoroalkyl substances in human tissues [J]. Environ Int, 2013, 59(3): 354–362.

[10] GÓRALCZYK K, PACHOCKI KA, HERNIK A, *et al*. Perfluorinated chemicals in blood serum of inhabitants in central Poland in relation to gender and age [J]. Sci Total Environ, 2015, 532: 548–555.

[11] AWAD R, ZHOU YH, NYBERG E, *et al*. Emerging per- and polyfluoroalkyl substances (PFAS) in human milk from Sweden and China [J]. Environ Sci Process Impacts, 2020, 22(10): 2023–2030.

[12] GURUGE KS, TANIYASU S, YAMASHITA N, *et al*. Perfluorinated organic compounds in human blood serum and seminal plasma: A study of urban and rural tea worker populations in Sri Lanka [J]. J Environ Monitor, 2005, 7(4): 371–377.

[13] WANG JH, PAN YT, WEI XF, *et al*. Temporal trends in prenatal exposure (1998—2018) to emerging and legacy per- and polyfluoroalkyl substances (PFASs) in cord plasma from the Beijing Cord Blood Bank, China [J]. Environ Sci Technol, 2020, 54(20): 12850–12859.

[14] DOMINGO JL, JOGSTEN IE, ERIKSSON U, *et al*. Human dietary exposure to perfluoroalkyl substances in Catalonia, Spain. Temporal trend [J]. Food Chem, 2012, 135(3): 1575–1582.

[15] CONDER JM, HOKE RA, WOLF W, *et al*. Are PFCAs bioaccumulative? A critical review and comparison with regulatory criteria and persistent lipophilic compounds [J]. Environ Sci Technol, 2008, 42(4): 995–1003.

[16] JIAN X, GUO CS, ZHANG Y, *et al*. Bioaccumulation and trophic transfer of perfluorinated compounds in a eutrophic freshwater food web [J]. Environ Pollut, 2014, 184: 254–261.

[17] JOHANSSON JH, BERGER U, VESTERGREN R, *et al*. Temporal trends (1999—2010) of perfluoroalkyl acids in commonly consumed food items [J]. Environ Pollut, 2014, 188: 102–108.

[18] GUERRANTI C, PERRA G, CORSOLINI S, *et al*. Pilot study on levels of perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) in selected foodstuffs and human milk from Italy [J]. Food Chem, 2013, 140(1–2): 197–203.

[19] KATO S, ITOH S, YUASA M, *et al*. Association of perfluorinated chemical exposure in utero with maternal and infant thyroid hormone levels in the Sapporo cohort of Hokkaido Study on the Environment and Children's Health [J]. Environ Health Prev, 2016, 21(5): 334–344.

[20] SRLI JB, LG M, EKEREN L, *et al*. Per- and polyfluoroalkyl substances (PFASs) modify lung surfactant function and pro-inflammatory responses in human bronchial epithelial cells [J]. Toxicol In Vitro, 2019, 62: 104656.

[21] YUAN ZQ, SHAO XX, MIAO ZL, *et al*. Perfluorooctane sulfonate induced neurotoxicity responses associated with neural genes expression, neurotransmitter levels and acetylcholinesterase activity in planarians *Dugesia japonica* [J]. Chemosphere, 2018, 206: 150–156.

[22] DU GZ, HU JL, HUANG ZY, *et al*. Neonatal and juvenile exposure to perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS): Advance puberty onset and kisspeptin system disturbance in female rats [J]. Ecotox Environ Saf, 2019, 167: 412–421.

[23] WEN Y, MIRJI N, IRUDAYARAJ J. Epigenetic toxicity of PFOA and GenX in HepG2 cells and their role in lipid metabolism [J]. Toxicol In Vitro, 2020, 65: 112528.

[24] HAIMBAUGH A, WU CC, AKEMANN C, *et al*. Multi- and transgenerational effects of developmental exposure to environmental levels of PFAS and PFAS mixture in zebrafish (*Danio rerio*) [J]. Toxics, 2022, 10(6): 334.

[25] ROUTTI H, DIOT B, PANTI C, *et al*. Contaminants in Atlantic walruses in Svalbard Part 2: Relationships with endocrine and immune systems [J]. Environ Pollut, 2019, 246: 658–667.

[26] WEATHERLY LM, SHANE HL, LUKOMSKA E, *et al*. Systemic toxicity induced by topical application of heptafluorobutyric acid (PFBA) in a murine model [J]. Food Chem Toxicol, 2021, 156: 112528.

[27] VIEIRA VM, HOFFMAN K, SHIN HM, *et al*. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: A geographic analysis [J]. Environ Health Perspect, 2013, 121(3): 318–323.

[28] CHEN H, HAN JB, CHENG JY, *et al*. Distribution, bioaccumulation and trophic transfer of chlorinated polyfluoroalkyl ether sulfonic acids in the marine food web of Bohai, China [J]. Environ Pollut, 2018, 241: 504–510.

[29] BOONE JS, VIGO C, BOONE T, *et al*. Per- and polyfluoroalkyl substances in source and treated drinking waters of the United States [J]. Sci Total Environ, 2019, 653: 359–369.

[30] BAKER BB, HAIMBAUGH AS, SPERONE FG, *et al*. Persistent contaminants of emerging concern in a great lakes urban-dominant watershed [J]. J Great Lakes Res, 2022, 48(1): 171–182.

[31] United Nations Environment Programme. Report of the conference of the parties of the stockholm convention on persistent organic pollutants on the work of its fourth meeting [EB/OL]. [2009-05-08]. http: //www. pops. int/TheConvention/ConferenceoftheParties/Meetings/COP4/tabid/404/mctl/ViewDetails/EventModID/870/EventID/23/xmid/1673/Default. aspx [2022-07-09].

[32] United Nations Environment Programme. Report of the conference of the parties to the stockholm convention on persistent organic pollutants on the work of its ninth meeting [EB/OL]. [2019-06-27]. http://www. pops. int/TheConvention/ConferenceoftheParties/Meetings/COP9/tabid/7521/Default. aspx [2022- 07-09].

[33] United Nations Environment Programme. Decision POPRC-15/1: Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds [EB/OL]. [2022-06-17]. http://chm. pops. int/TheConvention/ThePOPs/ChemicalsProposedforListing/tabid/2510/Default. aspx [2022-07-09].

[34] WU YM, DENG M, JIN YX, *et al*. Toxicokinetics and toxic effects of a Chinese PFOS alternative F-53B in adult zebrafish [J]. Ecotox Environ Saf, 2019, 171: 460–466.

[35] WU RB, LIN HJ, YAMAZAKI E, *et al*. Simultaneous analysis of neutral and ionizable per- and polyfluoroalkyl substances in air [J]. Cheosphere, 2021, 280: 130607.

[36] WANG Q, RUAN YF, LIN HJ, *et al*. Review on perfluoroalkyl and polyfluoroalkyl substances (PFASs) in the Chinese atmospheric environment [J]. Sci Total Environ, 2020, 737: 139804.

[37] PAN YT, ZHANG HX, CUI QQ, *et al*. Worldwide distribution of novel perfluoroether carboxylic and sulfonic acids in surface water [J]. Environ Sci Technol, 2018, 52(14): 7621–7629.

[38] ZHANG B, HE Y, HUANG YY, *et al*. Novel and legacy poly- and perfluoroalkyl substances (PFASs) in indoor dust from urban, industrial, and e-waste dismantling areas: The emergence of PFAS alternatives in China [J]. Environ Pollut, 2020, 263A: 114461.

[39] SI YY, HUANG JK, LIANG ZH, *et al*. Occurrence and ecological risk assessment of perfluoroalkyl substances (PFASs) in water and sediment from an urban river in South China [J]. Arch Environ Contam Toxicol, 2021, 81(1): 133–141.

[40] WANG JX, SHI GH, YAO JZ, *et al*. Perfluoropolyether carboxylic acids (novel alternatives to PFOA) impair zebrafish posterior swim bladder development via thyroid hormone disruption [J]. Environ Int, 2020, 134: 105317.

[41] CUI QQ, PAN YT, ZHANG HX, *et al*. Occurrence and tissue distribution of novel perfluoroether carboxylic and sulfonic acids and legacy per/polyfluoroalkyl substances in black-spotted frog (*Pelophylax nigromaculatus*) [J]. Environ Sci Technol, 2018, 52(3): 982–990.

[42] SAMMI SR, FOGUTH RM, NIEVES CS, *et al*. Perfluorooctane sulfonate (PFOS) produces dopaminergic neuropathology in caenorhabditis elegans [J]. Toxicol Sci, 2019, 172(2): 417–434.

[43] SPULBER S, KILIAN P, IBRAHIM WNW, *et al*. PFOS Induces behavioral alterations, including spontaneous hyperactivity that is corrected by dexamfetamine in zebrafish larvae [J]. PLoS One, 2014, 9(4): e94227.

[44] HUANG HH, HUANG CJ, WANG LJ, *et al*. Toxicity, uptake kinetics and behavior assessment in zebrafish embryos following exposure to perfluorooctanesulphonicacid (PFOS) [J]. Aquat Toxicol, 2010, 98(2): 139–147.

[45] JANTZEN CE, ANNUNZIATO KA, BUGEL SM, *et al*. PFOS, PFNA, and PFOA sub-lethal exposure to embryonic zebrafish have different toxicity profiles in terms of morphometrics, behavior and gene expression [J]. Aquat Toxicol, 2016, 175: 160–170.

[46] ULHAQ M, ÖRN S, CARLSSON G, *et al*. Locomotor behavior in zebrafish (*Danio rerio*) larvae exposed to perfluoroalkyl acids [J]. Aquat Toxicol, 2013, 144–145(8): 332–340.

[47] GUO XC, ZHANG SN, LU SY, *et al*. Perfluorododecanoic acid exposure induced developmental neurotoxicity in zebrafish embryos [J]. Environ Pollut, 2018, 241: 1018–1026.

[48] MENGER F, POHL J, AHRENS L, *et al*. Behavioural effects and bioconcentration of per- and polyfluoroalkyl substances (PFASs) in zebraflsh (*Danio rerio*) embryos [J]. Chemosphere, 2020, 245: 125573.

[49] TUKKER AM, BOUWMAN LMS, KLEEF RGDMV, *et al*. Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) acutely affect human $\alpha_1\beta_2\gamma_{2L}$ GABAA receptor and spontaneous neuronal network function *in vitro* [J]. Sci Rep, 2020, 10(1): 5311.

[50] NISIO A, PANNELLA M, VOGIATZIS S, *et al*. Impairment of human dopaminergic neurons at different developmental stages by perfluoro-octanoic acid (PFOA) and differential human brain areas accumulation of perfluoroalkyl chemicals [J]. Environ Int, 2022, 158: 106982.

[51] SHANE HL, BAUR R, LUKOMSKA E, *et al*. Immunotoxicity and allergenic potential induced by topical application of perfluorooctanoic acid (PFOA) in a murine model [J]. Food Chem Toxicol, 2020, 136: 111114.

[52] TORRES L, REDKO A, LIMPER C, *et al*. Effect of perfluorooctanesulfonic acid (PFOS) on immune cell development and function in mice [J]. Immunol Lett, 2021, 233: 31–41.

[53] CASTANO-ORTIZ JM, JASPERS VLB, WAUGH CA. PFOS mediates immunomodulation in an avian cell line that can be mitigated via a virus infection [J]. BMC Vet Res, 2019, 15: 214.

[54] SANT KE, VENEZIA OL, SINNO PP, *et al*. Perfluorobutanesulfonic acid disrupts pancreatic organogenesis and regulation of lipid metabolism in the zebrafish, *Danio rerio* [J]. Toxicol Sci, 2019, 167(1): 258–268.

[55] SANT KE, ANNUNZIATO K, CONLIN S, *et al*. Developmental exposures to perfluorooctanesulfonic acid (PFOS) impact embryonic nutrition, pancreatic morphology, and adiposity in the zebrafish, *Danio rerio* [J]. Environ Pollut, 2021, 275: 116644.

[56] ROTH K, YANG Z, AGARWAL M, *et al*. Exposure to a mixture of legacy, alternative, and replacement per- and polyfluoroalkyl substances (PFAS) results in sex-dependent modulation of cholesterol metabolism and liver injury [J]. Environ Int, 2021, 157: 106843.

[57] PFOHL M, INGRAM L, MARQUES E, *et al*. Perfluorooctanesulfonic acid and perfluorohexanesulfonic acid alter the blood lipidome and the hepatic proteome in a murine model of diet-inducedobesity [J]. Toxicol Sci, 2020, 178(2): 311–324.

[58] ZHANG SH, CHEN K, LI WM, *et al*. Varied thyroid disrupting effects of perfluorooctanoic acid (PFOA) and its novel alternatives hexafluoropropylene-oxide-dimer-acid (GenX) and ammonium 4, 8-dioxa-3H-perfluorononanoate (ADONA) *in vitro* [J]. Environ Int, 2021, 156: 106745.

[59] CONTI A, STRAZZERI C, RHODEN KJ. Perfluorooctane sulfonic acid, a persistent organic pollutant, inhibits iodide accumulation by thyroid follicular cells *in vitro* [J]. Mol Cell Endocrinol, 2020, 515: 110922.

[60] BEHR AC, LICHTENSTEIN D, BRAEUNING A, *et al*. Perfluoroalkylated substances (PFAS) affect neither estrogen and androgen receptor activity nor steroidogenesis in human cells *in vitro* [J]. Toxicol Lett, 2018, 291: 51–60.

[61] CHEN FJ, WEI CY, CHEN QY, *et al*. Internal concentrations of perfluorobutane sulfonate (PFBS) comparable to those of perfluorooctane sulfonate (PFOS) induce reproductive toxicity in *Caenorhabditis elegans* [J]. Ecotox Environ Saf, 2018, 158: 223–229.

[62] POTESER M, HUTTER HP, MOSHAMMER H, *et al*. Perfluoroctanoic acid (PFOA) enhances NOTCH-signaling in an angiogenesis model of placental trophoblast cells [J]. Int J Hyg Environ Health, 2020, 229: 113566.

[63] BANGMA J, SZILAGYI J, BLAKE BE, *et al*. An assessment of serum-dependent impacts on intracellular accumulation and genomic response of per- and polyfluoroalkyl substances in a placental trophoblast model [J]. Environ Toxicol, 2020, 35(12): 1395–1405.

[64] WANG SW, HUANG J, YANG Y, *et al*. First report of a Chinese PFOS alternative overlooked for 30 years: Its toxicity, persistence, and presence in the environment [J]. Environ Sci Technol, 2013, 47(18): 10163–10170.

[65] 张美, 楼巧婷, 邵倩文, 等. 全氟化合物污染现状及风险评估的研究进展[J]. 生态毒理学报, 2019, 14(3): 24.
ZHANG M, LOU QT, SHAO QW, *et al*. Research progress of perfluorinated compounds pollution status and risk assessment [J]. Asian J Ecotoxicol, 2019, 14(3): 24.

[66] GEBBINK WA, ASSELDONK L, LEEUWEN SPJ. Presence of emerging per- and polyfluoroalkyl substances (PFASs) in river and drinking water near a fluorochemical production plant in the netherlands [J]. Environ Sci Technol, 2017, 51(19): 11057–11065.

[67] WANG Y, SHI YL, CAI YQ. Spatial distribution, seasonal variation and risks of legacy and emerging per- and polyfluoroalkyl substances in urban surface water in Beijing, China [J]. Sci Total Environ, 2019, 673: 177–183.

[68] CHEN H, MUNOZ G, DUY SV, *et al*. Occurrence and distribution of per- and polyfluoroalkyl substances in Tianjin, China: The contribution of emerging and unknown analogues [J]. Environ Sci Technol, 2020, 54(22): 14254–14264.

[69] LIU W, QIN H, LI JW, *et al*. Atmospheric chlorinated polyfluorinated ether sulfonate and ionic perfluoroalkyl acids in 2006 to 2014 in Dalian, China: Airborne ionic PFAAs and the alternative Cl-PFESA [J]. Environ Toxicol Chem, 2017, 36(10): 2581–2586.

[70] FENG XM, YE MQ, LI Y, *et al*. Potential sources and sediment-pore water partitioning behaviors of emerging per/polyfluoroalkyl substances in the South Yellow Sea [J]. J Hazard Mater, 2020, 389: 122124.

[71] RUAN T, LIN YF, WANG T, *et al*. Identification of novel polyfluorinated ether sulfonates as PFOS alternatives in municipal sewage sludge in China [J]. Environ Sci Technol, 2015, 49(11): 6519–6527.

[72] GUO JQ, ZHANG JM, WANG Z, *et al*. Umbilical cord serum perfluoroalkyl substance mixtures in relation to thyroid function of newborns: Findings from sheyang mini birth cohort study [J]. Chemosphere, 2021, 273: 129664.

[73] ANDROULAKAKIS A, ALYGIZAKIS N, GKOTSIS G, *et al*. Determination of 56 per- and polyfluoroalkyl substances in top predators and their prey from Northern Europe by LC-MS/MS [J]. Chemosphere, 2022, 287: 131775.

[74] LIU ML, DONG FF, YI SJ, *et al*. Probing mechanisms for the tissue-specific distribution and biotransformation of perfluoroalkyl phosphinic acids in common carp (*Cyprinus carpio*) [J]. Environ Sci Technol, 2020, 54(8): 4932–4941.

[75] YI SJ, ZHU LY, MABURY SA. First report on *in vivo* pharmacokinetics and biotransformation of chlorinated polyfluoroalkyl ether sulfonates in rainbow trout [J]. Environ Sci Technol, 2020, 54(1): 345–354.

[76] ANNUNZIATO KM, JANTZEN CE, GRONSKE MC, *et al*. Subtle morphometric, behavioral and gene expression effects in larval zebrafish exposed to PFHxA, PFHxS and 6:2 FTOH [J]. Aquat Toxicol, 2019, 208: 126–137.

[77] WOODLIEF T, VANCE S, HU Q, *et al*. Immunotoxicity of per- and polyfluoroalkyl substances: Insights into short-chain PFAS exposure [J]. Toxics, 2021, 9(5): 100.

[78] THOMPSON CM, FITCH SE, RING C, *et al*. Development of an oral reference dose for the perfluorinated compound GenX [J]. J Appl Toxicol, 2019, 39(9): 1267–1282.

[79] CHAPPELL GA, THOMPSON CM, WOLFJC, *et al*. Assessment of the mode of action underlying the effects of GenX in mouse liver and implications for assessing human health risks [J]. Toxicol Pathol, 2020, 48(3): 494–508.

[80] BLAKE BE, COPE HA, HALL SM, *et al*. Evaluation of maternal, embryo, and placental effects in CD-1 mice following gestational Exposure to perfluorooctanoic acid (PFOA) or hexafluoropropylene oxide dimer acid (HFPO-DA or GenX) [J]. Environ Health Perspect, 2020, 128(2): 027006.

[81] COPERCHINI F, CROCE L, DENEGRI M, *et al*. Adverse effects of *in vitro* GenX exposure on rat thyroid cell viability, DNA integrity and thyroid-related genes expression [J]. Environ Pollut, 2020, 264: 114778.

[82] GUO H, WANG JH, YAO JZ, *et al*. Comparative hepatotoxicity of novel PFOA alternatives (perfluoropolyether carboxylic acids) on male mice [J]. Environ Sci Technol, 2019, 53(7): 3929–3937.

[83] CHEN JM, LI HY, YAO JZ, *et al*. Chronic exposure to PFO4DA and PFO5DoDA, two perfluoroalkyl ether carboxylic acids (PFECAs), suppresses hepatic stress signals and disturbs glucose and lipid metabolism in male mice [J]. J Hazard Mater, 2021, 411: 124963.

[84] YI SJ, CHEN PY, YANG LP, *et al*. Probing the hepatotoxicity mechanisms of novel chlorinated polyfluoroalkyl sulfonates to zebrafish larvae: Implication of structural specificity [J]. Environ Int, 2019, 133B: 105262.

[85] XIN Y, WAN B, YU BL, *et al*. Chlorinated polyfluoroalkylether sulfonic acids exhibit stronger estrogenic effects than perfluorooctane sulfonate by activating nuclear estrogen receptor pathways [J]. Environ Sci Technol, 2020, 54(6): 3455–3464.

[86] LIU W, YANG J, LI JW *et al*. Toxicokinetics and persistent thyroid hormone disrupting effects of chronic developmental exposure to chlorinated polyfluorinated ether sulfonate in Chinese rare minnow [J]. Environ Pollut, 2020, 263B: 114491.

[87] SHI GH, GUO H, SHENG N, *et al*. Two-generational reproductive toxicity assessment of 6:2 chlorinated polyfluorinated ether sulfonate (F-53B, a novel alternative to perfluorooctane sulfonate) in zebrafish [J]. Environ Pollut, 2018, 243B: 1517–1527.

[88] ZHOU J, LI M, LI JQ, *et al*. Bioavailability and bioaccumulation of 6:2 fluorotelomer sulfonate, 6:2 chlorinated polyfluoroalkyl ether sulfonates, and perfluorophosphinates in a soil-plant system [J]. J Agric Food Chem, 2020, 68(15): 4325–4334.

[89] JIN Q, SHI YL, CAI YQ. Occurrence and risk of chlorinated polyfluoroalkyl ether sulfonic acids (Cl-PFESAs) in seafood from markets in Beijing, China [J]. Sci Total Environ, 2020, 726: 138538.

[90] CUI QQ, PAN YT, ZHANG HX, *et al*. Elevated concentrations of perfluorohexanesulfonate and other per and polyfluoroalkyl substances in Baiyangdian Lake (China): Source characterization and exposure assessment [J]. Environ Pollut, 2018, 241: 684–691.

[91] CAI D, LI QQ, CHU C, *et al*. High trans-placental transfer of perfluoroalkyl substances alternatives in the matched maternal-cord blood serum: Evidence from a birth cohort study [J]. Sci Total Environ, 2020, 705: 135885.

[92] SHENG N, WANG JH, GUO Y, *et al*. Interactions of perfluorooctanesulfonate and 6:2 chlorinated polyfluorinated ether sulfonate with human serum albumin: A comparative study [J]. Chem Res Toxicol, 2020, 33(6): 1478–1486.

[93] WANG JH, PAN YT, CUI QQ, *et al*. Penetration of PFASs across the

blood cerebrospinal fluid barrier and its determinants in humans [J]. Environ Sci Technol, 2018, 52(22): 13553–13561.

[94] CHU C, ZHOU Y, LI QQ, *et al*. Are perfluorooctane sulfonate alternatives safer? New insights from a birth cohort study [J]. Environ Int, 2020, 135: 105365.

[95] DUAN YS, SUN HW, YAO YM, *et al*. Distribution of novel and legacy per-/polyfluoroalkyl substances in serum and its associations with two glycemic biomarkers among Chinese adult men and women with normal blood glucose levels [J]. Environ Int, 2020, 134: 105295.

[96] JIN Q, MA JH, SHI YL, *et al*. Biomonitoring of chlorinated polyfluoroalkyl ether sulfonic acid in the general population in central and eastern China: Occurrence and associations with age/sex [J]. Environ Int, 2020, 144: 106043.

[97] LIU JY, GAO XY, WANG YX, *et al*. Profiling of emerging and legacy per-/polyfluoroalkyl substances in serum among pregnant women in China [J]. Environ Pollut, 2021, 271: 116376.

[98] LIU HX, PAN YT, JIN SN, *et al*. Associations between six common per- and polyfluoroalkyl substances and estrogens in neonates of China [J]. J Hazard Mater, 2021, 407: 124378.

[99] PAN YT, ZHU YS, ZHENG TZ, *et al*. Novel chlorinated polyfluorinated ether sulfonates and legacy per-/polyfluoroalkyl substances: Placental transfer and relationship with serum albumin and glomerular filtration rate [J]. Environ Sci Technol, 2017, 51(1): 634–644.

[100] KOTLARZ N, MCCORD J, COLLIER D, *et al*. Measurement of novel, dinking water-associated PFAS in blood from adults and children in Wilmington, North Carolina [J]. Environ Health Perspect, 2020, 128(7): 077005.

[101] YAO JZ, PAN YT, SHENG N, *et al*. Novel perfluoroalkyl ether carboxylic acids (PFECAs) and sulfonic acids (PFESAs): Occurrence and association with serum biochemical parameters in residents living near a fluorochemical plant in China [J]. Environ Sci Technol, 2020, 54(21): 13389–13398.

[102] WANG Y, SHI Y, VESTERGREN R, *et al*. Using hair, nail and urine samples for human exposure assessment of legacy and emerging per- and polyfluoroalkyl substances [J]. Sci Total Environ, 2018, 636: 383–391.

[103] KANG QY, GAO FM, ZHANG XH, *et al*. Nontargeted identification of per- and polyfluoroalkyl substances in human follicular fluid and their blood-follicle transfer [J]. Environ Int, 2020, 139: 105686.

[104] CUI QQ, PAN YT, WANG JH, *et al*. Exposure to per- and polyfluoroalkyl substances (PFASs) in serum versus semen and their association with male reproductive hormones [J]. Environ Pollut, 2020, 266: 115330.

[105] LU Y, MENG LY, MA DH, *et al*. The occurrence of PFAS in human placenta and their binding abilities to human serum albumin and organic anion transporter 4 [J]. Environ Pollut, 2021, 273: 116460.

[106] NIAN M, HUO XN, ZHANG JT, *et al*. Association of emerging and legacy per- and polyfluoroalkyl substances with unexplained recurrent spontaneous abortion [J]. Ecotox Environ Saf, 2022, 239: 113691.

[107] JIN HB, MAO LL, XIE JH, *et al*. Poly- and perfluoroalkyl substance concentrations in human breast milk and their associations with postnatal infant growth [J]. Sci Total Environ, 2020, 713: 136417.

[108] YU S, FENG WR, LIANG ZMA, *et al*. Perfluorooctane sulfonate alternatives and metabolic syndrome in adults: New evidence from the isomers of C8 health project in China [J]. Environ Pollut, 2021, 283: 117078.

[109] HAN X, MENG LL, ZHANG GX, *et al*. Exposure to novel and legacy per- and polyfluoroalkyl substances (PFASs) and associations with type 2 diabetes: A case-control study in East China [J]. Environ Int, 2021, 156: 106637.

[110] CONG JP, CHU C, LI QQ, *et al*. Associations of perfluorooctane sulfonate alternatives and serum lipids in Chinese adults [J]. Environ Int, 2021, 155: 106569.

[111] ZENG XW, LI QQ, CHU C, *et al*. Alternatives of perfluoroalkyl acids and hepatitis B virus surface antibody in adults: Isomers of C8 Health Project in China [J]. Environ Pollut, 2020, 259: 113857.

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