Eco-Environmental Knowledge Web

环 境 化 学
ENVIRONMENTAL CHEMISTRY

第 40 卷第 5 期 2021 年 5 月
Vol. 40, No. 5 May 2021

DOI:10.7524/j.issn.0254-6108.2020082402

王梦圆, 张龙飞, 汤云瑜, 等. 几种水生模式生物在持久性有机污染物毒理学评价中的研究进展[J]. 环境化学, 2021, 40(5): 1361-1378.
WANG Mengyuan, ZHANG Longfei, TANG Yunyu, et al. Research progress of several aquatic biological models in toxicological evaluation of persistent organic pollutants[J]. Environmental Chemistry, 2021, 40 (5): 1361-1378.

几种水生模式生物在持久性有机污染物毒理学评价中的研究进展*

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摘 要 持久性有机污染物对环境及生物体产生的危害已引起全球范围内的持续关注. 此类物质能够富集在生物体内，并通过食物链传递产生生物放大效应，进而引发“三致”作用、发育毒性、内分泌干扰效应等. 水生模式生物具有饲养成本低、生理周期较短、繁殖量大等优点而被广泛应用于 POPs 毒理学评价. 本文聚焦斑马鱼、青鳉鱼、非洲爪蟾等几种水生模式生物，对其在 POPs 毒性效应研究中的应用进展进行综述，包括 POPs 所致骨骼发育畸形、心血管系统病变、性腺发育异常等发育毒性，卵黄蛋白原的诱导、性腺指数、甲状腺激素水平的改变等内分泌干扰效应以及神经行为异常等相关研究内容，希望为 POPs 污染现状评估以及毒理效应的深入探索、疾病预测模型的建立提供资料参考，并对该领域研究过程中生物模型的筛选具有借鉴意义.

关键词 水生模式生物，持久性有机污染物，斑马鱼，青鳉鱼，非洲爪蟾，毒理效应.

Research progress of several aquatic biological models in toxicological evaluation of persistent organic pollutants

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Abstract The harm of persistent organic pollutants (POPs) to the environment and organisms has attracted continuous attention all over the world. Such substances can be enriched in organisms and produce biological amplification effect through food chain transmission, which in turn triggers “three toxicity” effects, developmental toxicity, endocrine disrupting effects, etc. Aquatic model organisms have been widely used in toxicological evaluation of POPs because of their low feeding cost, short physiological cycle and large reproduction. In this paper, several aquatic biological models, such as zebrafish (*Danio rerio*), medaka (*Oryzias latipes*) and *Xenopus laevis*, are focused on to review the

2020 年 8 月 24 日收稿(Received：August 24，2020).

* 农业部公益性行业（农业）科研专项（201503108）和国家自然科学基金（31501572）资助.
Supported by Agriculture Industry Research Special Funds for Public Welfare Projects (201503108) and the National Natural Science Foundation of China (31501572).

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application of these models in the study of toxic effects caused by POPs. These toxic effects include developmental toxicity such as skeletal malformation, cardiovascular diseases, gonadal dysplasia, reproductive endocrine disrupting effects such as vitellogenin induction, gonadal index and thyroid hormone levels, as well as neurobehavioral abnormalities and other related research contents. We hope to provide reference for the assessment of POPs pollution status, the in-depth exploration of the toxicological effects of POPs, and establishment of disease prediction model. At the same time, it provides reference for the screening of biological models in the research process of this field.

Keywords aquatic biological models, persistent organic pollutants, *Danio rerio*, *Oryzias latipes*, *Xenopus laevis*, toxicological effects.

《关于持久性有机污染物的斯德哥尔摩公约》(以下简称 POPs 公约)是人类历史上为保护全球生态环境而签订的第三个具有强制性的国际公约[1]. 自 2001 年 POPs 公约签订, 到 2019 年公约缔约方大会第九次会议召开, POPs 名录已扩充至 28 种[2－5]. 据统计, 国内在上世纪 80 年代之前有数十万吨的有机氯农药(organochlorine pesticides, OCPs)通过各种途径进入土壤和水体[6]; 曾被各国广泛应用于电力、化工等领域的多氯联苯(polychlorinated biphenyls, PCBs), 有近 40 万吨进入环境并造成严重生态问题[7－9]. 在工业现代化进程中, 大量多氯二苯并二噁英(polychlorinated dibenzodioxin, PCDD)、多氯二苯并呋喃(polychlorinated dibenzofuran, PCDF)、多溴二苯醚(polybrominated diphenyl ethers, PBDEs)以及多氟烷基化合物(polyfluoroalkyl compounds, PFCs)等 POPs 持续泄露或排放到环境中[10－14]. 由于 POPs 具有持久残留性并能进行远距离迁移, 有学者已在上万米深的海底沉积物中发现 PCBs、PBDEs、二噁英等 POPs 的存在[15].

POPs 是一类具有生物蓄积性和毒性效应的化合物, 能够对生物体产生危害. 上世纪六七十年代在日本及我国台湾发生的“米糠油”事件以及 1999 年发生在比利时的二噁英食品污染事件, 是 POPs 污染危害生物体健康的典型案例[16－18]. 生物体长期接触 POPs 后, 可引起骨骼发育畸形, 同时脑、心脏等组织器官在生长发育过程中可出现病变[19－20], 机体正常内分泌及代谢功能也会受到干扰, 并可导致糖尿病等疾病的发生[21－22]. 即使在低水平的暴露下, POPs 仍能表现出诸如神经毒性等效应, 造成生物体的行为、学习、运动等方面出现异常[23－24]. POPs 通过食物链产生生物放大效应, 因此需要对 POPs 毒理学效应进行深入研究.

在毒理学研究中, 生物模型的应用是揭示外源化合物毒理机制的一种有效手段. 近年来, 随着研究人员对 POPs 等外源化合物毒理效应研究的不断推进, 一些水生生物作为模式生物不断被开发应用. 其中斑马鱼、青鳉鱼、非洲爪蟾在过去上百年时间被广泛应用于生理学、胚胎学以及毒理学研究, 操作技术相对成熟[25－30]. 相比于其他水生模式生物, 这三种模式生物具有体型较小、产卵周期可控且产卵量大、对外源化合物刺激敏感等特点, 有利于 POPs 毒理学研究的开展[26, 31－32]. 以水生生物为模型研究 POPs 的毒理学效应, 不仅能够降低实验成本、提高实验效率, 更能反映水环境中的真实污染状况[33－34]. 因此, 本文综述了水生模式生物在 POPs 毒理效应研究中的应用进展, 对深入探索 POPs 的毒理学效应机制、实验动物模型的筛选以及水环境污染治理工作的开展具有重要的参考价值.

1 水生模式生物在 POPs 发育毒性研究中的应用(Application of aquatic biological models in the study of developmental toxicity of POPs)

POPs 具有亲脂性, 进入生物体后代谢速率较慢, 可影响机体的正常生长发育[35－36]. 有学者跟踪调查了一批在孕期接触 PCBs 的女性, 发现 PCBs 能够通过胎盘转移至婴儿, 干扰子代儿童时期的正常发育, 并导致青春期发育延迟[37]. 受 POPs 污染影响的鸟类, 其鸣管等发声系统可能会出现异常发育, 进而与同类之间的正常交流受到影响[38]. POPs 引起的发育毒性已经对各类生物的生存造成威胁, 鉴于水生生物的生理周期相对较短, 繁殖量大, 胚胎发育较快并且易观察, 因此水生模式生物在 POPs 发育毒性效应的研究中逐渐被推广使用[31].

1.1　斑马鱼

斑马鱼(*Danio rerio*)饲养条件相对简单, 作为一种毒理学研究的经典水生模式生物, 与人类分享87% 的同源基因, 在化合物毒理学效应的评估、疾病模型预测等多数实验结果可推广至人体[39－40]. 斑马鱼胚胎已发展成为重要的脊椎动物模型, 适用于遗传学、胚胎学、发育和细胞生物学的研究[41]. 仔鱼在受精 2—3 d 后孵化, 3—4 月可达性成熟, 在 TCDD 等外源化合物的处理下, 受精后 72 h 内可辨认出 20 多种不同的毒理学终点, 被广泛应用于发育毒理学的研究[19, 25, 29, 42]. 而成年斑马鱼在 POPs 蓄积毒性、基因表达、行为研究等方面同样得到广泛应用[43－44]. 近二十年来利用斑马鱼开展的关于 POPs 发育毒性的实验研究及其主要结果见表 1.

表 1　斑马鱼在 POPs 发育毒性研究中的应用

Table 1　Application of zebrafish in POPs developmental toxicity studies

物质 Substances	暴露浓度 Exposure concentration	暴露时间 Exposure time	发育毒性 Developmental toxicity	文献 References
TCDD	1.50 ng·g^{-1}卵	12—240 hpf	心包水肿, 颅面畸形, 卵黄囊水肿和死亡	[45]
	1 nmol·L^{-1}	0—24 hpf	颌骨发育被阻断, 出现颅面畸形	[46]
	0.005 nmol·L^{-1}	0—48 hpf	与肿瘤相关基因的表达水平受到调控	[47]
	1.00 ng·mL^{-1}	0—120 hpf	抑制心外膜的发育与扩张, 出现心力衰竭	[48]
	1.00 ng·mL^{-1}	0—120 hpf	心室紧凑, 心房狭长, 心肌细胞总数减少, 出现心室停顿	[49]
BDE47	100—5 000 mg·L^{-1}	0—96 hpf	身体背侧及后脑弯曲, 房室传导阻滞性心律失常	[50]
	10.0、5.0、2.5、0.635 mg·L^{-1}	0—168 hpf	体轴弯曲, 发育畸形, 并出现死亡	[51]
	5、10、50 ng·L^{-1}	0—96 hpf	发育抑制, 氧化应激, 细胞凋亡和DNA损伤	[52]
	0.06、0.20、0.60 nmol·L^{-1}	2—72 hpf	主静脉的生长略有下降, 肠下及卵黄血管化面积显著减少	[53]
BDE49	4—32 mmol·L^{-1}	0—144 hpf	尾部背侧弯曲, 心率显著降低	[54]
BDE 71	0、31.0、68.7、227.6 mg·L^{-1}	2—120 hpf	视黄酸含量明显降低, 眼球发育受阻	[55]
PCBs	>0.25 mg·L^{-1}	0—96 hpf	视网膜、感光细胞层厚度均明显增厚, 感光层细胞排列紊乱	[56]
	1.00 mg·L^{-1}	0—120 hpf	脊柱弯曲畸形, 存活率降低	[57]
	1.00 mg·L^{-1}	0—96 hpf	形态畸变, 视网膜层发育被延迟	[58]
	0.25 mg·L^{-1}	0—96 hpf	形态畸变, 感光细胞排列不规则以及感光层增厚	
	0、0.125、0.50、1.0 mg·L^{-1}	0—120 hpf	与骨形成、胚胎发育相关基因的表达被抑制, 骨骼发育缺陷	[59]
	0.25、0.5、0.75、1 μg·L^{-1}	0—120 hpf	形态畸形, 脑细胞坏死, 眼睛发育较小	[20]
	0.125、0.25、0.50、1 mg·L^{-1}	0—168 hpf	与感光细胞发育相关基因的表达下调, 感光行为发生改变	[60]
	32 μg·L^{-1}	0—144 hpf	幼鱼心包卵黄囊水肿率显著增加	[61]
	>125 μg·L^{-1}	0—48 hpf	胚胎发育畸形及延迟, 心脏形态发育异常	[19]
PFOS	0、367、1834、3 668、18 338、36 676 ng·g−1(胚胎湿重)	0—96 hpf	延迟孵化和脊柱弯曲, 胚胎发育异常或死亡	[62]
	1、3、5 mg·L^{-1}	4—132 hpf	孵化延迟, 孵化率和存活率显著降低, 发育畸形	[63]

注: TCDD表示Tetrachlorodibenzo-*p*−dioxin, 四氯二苯并-*p*−二噁英.; hpf 表示hours post fertilization, 受精后小时数.; PFOS表示Perfluorooctane sulfonate, 全氟辛烷磺酸盐.

通过表 1 研究结果发现, 在利用斑马鱼评价 POPs 发育毒性时, 以胚胎为模型开展的研究最为广泛, 相关研究充分利用了斑马鱼胚胎体外发育、透明且易观察等优势[29]. POPs 的毒性终点主要集中在造成心脏的发育和功能异常、胚胎畸形、发育延迟以及视力干扰等, 可导致斑马鱼心包水肿、心力衰竭, 体轴弯曲, 孵化延迟, 视网膜增厚、眼球发育较小等[45, 48, 51, 58].

1.2　青鳉鱼

青鳉鱼(*Oryzias latipes*)是来自东亚地区的小型鱼种, 卵子和胚胎均透明, 生长发育过程对水环境中的污染物较为敏感, 所产生的毒理效应终点易于观察监测, 在评价外源化合物对动物产生的发育毒性效应中应用较为广泛[64]. 青鳉对盐度、温度以及常见鱼类疾病的耐受力较强, 孵化后 2 个月达到性成熟[26, 65].

研究表明，青鳉鱼的胚胎能够对二噁英类化合物作出敏感应答[66]. 以青鳉鱼为模型，Dong 等和 Kawamura 等评估了 TCDD 对骨骼发育的影响，他们发现暴露于 TCDD 会导致椎骨骨化总体衰减，通过干扰成骨细胞的分化及其基因表达抑制，影响骨骼的正常发育与形成[67－68]. 进一步研究发现，TCDD 能够对青鳉胚胎血管以及血液凝固产生影响，并导致骨骼发育畸形[69]. Cantrell 等[70] 利用青鳉鱼胚胎对 TCDD 的胚胎发育毒性做了深入探讨，他们发现暴露于 TCDD 的胚胎卵黄内侧静脉中均容易出现凋亡细胞，并推断这种现象可作为野生生物接触二噁英类化合物的标志. 而将发育中的青鳉鱼胚胎同时暴露于 TCDD 和 PCBs 时，可对心血管系统产生毒性作用，并能观察到多灶性出血、心包和卵黄囊水肿、颅面畸形和鱼鳔膨胀受阻等病变现象[71].

此外，青鳉鱼在多种 POPs 发育毒性的研究中均有应用. 利用青鳉胚胎研究 PFOS 对动物心脏发育的毒性效应时，将受精 2 d 后的胚胎持续暴露于 PFOS，结果表明，在 PFOS 浓度超过 4 mg·L^{-1} 时会导致静脉窦和大动脉球之间的距离增大，并引起心律失常，从而影响心脏的发育和功能[72]. 利用卵内纳米注射技术研究 POPs 与重金属对青鳉胚胎发育和孵化的综合毒性，发现三丁基锡（tributyltin, TBT）和 PCB 混合物会引发卵黄囊收缩，胚胎孵化延迟，幼仔发育畸形率增加，游泳上浮受阻[73－74]. 以同样的方式向青鳉鱼胚胎注射暴露 1, 1-二氯-2-（对氯苯基）-2-（邻氯苯基）乙烯 [1, 1-dichloro-2-(*p*-chlorophenyl)-2-(*o*-chlorophenyl) ethylene, DDE]，对其进行监测直至性成熟，观察到死亡前青鳉体内发生心血管病变和脊柱畸形[75]. 另外有研究显示，双对氯苯基三氯乙烷 (dichlorodiphenyltrichloroethane, DDT) 及其主要代谢产物 DDE 的暴露会导致青鳉鱼性腺异常发育[76－77].

在评价 POPs 不同暴露剂量对青鳉鱼发育造成的影响时发现，幼鱼孵化死亡率增加，骨骼发育出现畸形或缺陷，心、肝、鱼鳔以及性腺等组织器官出现不同程度的功能失常，其生长发育过程受到不利影响. 与斑马鱼类似，青鳉鱼的受精卵、胚胎在 POPs 发育毒理效应研究中不断被开发利用. 通过对暴露青鳉鱼生命周期的持续性观察，能够较好地研究 POPs 对动物体发育过程中产生的影响.

1.3 非洲爪蟾

非洲爪蟾（*Xenopus laevis*）原产自南非，体长 6—13 cm，雄性个体大小约为雌性的一半，在实验室条件下可存活 15 年左右[27]. 非洲爪蟾胚胎体外发育，胚体较大且早期发育速度较快，其变态发育过程容易受到环境中外源化学物质的干扰，这些特点决定了非洲爪蟾可作为一种理想的动物模型应用于发育毒理研究[78－79].

以非洲爪蟾为模型探讨 PCBs 对两栖动物发育的影响，发现 PCBs 导致的发育畸形或死亡与暴露阶段及观察周期的长短有关，部分实验研究结果可能低估 PCBs 等污染物对两栖动物的毒性作用[80]. 将受精卵暴露在一定浓度的 Aroclor 1254 中直至变态完全，甲状腺发育出现明显的组织学变化，且该变化与 PCBs 呈剂量效应关系[81－82]. 甲状腺发育异常在一定条件下可能直接导致非洲爪蟾蝌蚪变态发育延迟，这可能与 PCBs 诱导的氧化应激、能量代谢的适应性改变以及某些细胞蛋白的合成有关[83]. 进一步研究显示，PCBs 的暴露不仅引起蝌蚪的变态发育延迟、畸形或死亡，还可导致组织学异常，包括尾端出现肌瘤和黑素细胞形态[84]. 变态发育完成后的非洲爪蟾暴露于 PCBs，性腺发育表型雌性化，实验组雄蛙长出输卵管，且软骨和肌肉的发育受到抑制[85].

TCDD 和卤代芳烃的毒性主要是由芳香烃受体（AhR）介导的，AhR 信号通路特性的差异可能是 TCDD 产生不同毒性的基础. Lavine 等[86] 研究表明，非洲爪蟾体内表达的 AhR1α 和 AhR1β 与 TCDD 的亲和力比小鼠低 20 倍，而 Philips 等发现幼蟾在发育后期体内存在对 TCDD 的清除作用，这些可能是蛙类对于 TCDD 相对不敏感的原因[87]. Sakamoto 等[88] 研究发现暴露于 TCDD 的非洲爪蟾消化道发育异常，肠腔脱落导致粘膜上皮细胞丢失，可能是由于 TCDD 的暴露使得幼蟾肠道主要细胞发生明显的凋亡.

相比于其他生物，POPs 诱发的发育毒性效应对非洲爪蟾相对不敏感，但对其变态发育的影响最显著. 长期接触到 POPs 的非洲爪蟾在发育过程中会出现发育延迟、畸形或死亡，甲状腺、消化道等组织器官出现异常. 以 POPs 引起的变态发育异常为突破口进行深入探索，能够为进一步阐明 POPs 的发育毒理机制提供科学论据.

2　水生模式生物在 POPs 内分泌干扰效应研究中的应用(Application of aquatic biological models in the study of endocrine disrupting effects of POPs)

PCBs、OCPs 等 POPs 与体内雌激素、甲状腺激素(thyroid hormone, TH)等内分泌物质的化学结构相似, 能够通过竞争性抑制干扰这些激素在体内的正常水平, 或通过影响其受体活性造成机体内分泌功能紊乱[89－90], 这些物质可归为内分泌干扰物(endocrine disruptors, EDs). 鱼类等水生脊椎动物的生理系统与哺乳动物较为相似, 以其为模型研究 POPs 的内分泌干扰作用, 结果可推广至其它脊椎动物[91]. 研究者在实验室可通过投饵、注射或浸浴等方式将污染物暴露于水生生物体, 也能直接在指定地区自然环境中进行实验, 尤其是一些小型鱼类, 便于转移和实验条件的变换, 是研究 POPs 内分泌干扰效应的理想动物模型.

2.1　斑马鱼

POPs 通过干扰内分泌影响生物体代谢、生殖等功能, 造成生物体生存和繁殖能力降低. 已有的研究证明, 利用斑马鱼评价 POPs 的内分泌干扰效应时, 实验灵敏度高, 应用技术相对成熟[92]. 卵黄蛋白原(vitellogenin, VTG)的诱导水平、性腺指数(gonadosomatic index, GSI)、产卵数以及各激素水平等是利用斑马鱼评价 POPs 内分泌干扰效应的常用指标[93－94].

PCBs 能够通过与部分激素受体的竞争性结合产生内分泌干扰效应[95]. 将处于性腺分化关键时期(30—44 dpf)的斑马鱼幼鱼暴露在 PCB77 的环境中, 其体内 VTG 表达受到抑制, GSI 减小, 可能对繁殖产生进一步影响[96]. 为研究污染物对 TH 的干扰效应, Chen 等[97] 对暴露 PCBs 的斑马鱼体内 TH 进行了检测, 结果发现甲状腺素 (T4)与三碘甲状腺素(T3)的比率增加, 而 T3 与 3,3', 5'-三碘-1-甲状腺素的比率有所减小. 长期接触 PCBs、PBDEs 等 POPs 混合物的斑马鱼, 卵泡发育、肝脏卵黄原蛋白免疫染色强度均出现被抑制的情况[98]. PBDEs 还可通过影响生殖行为降低斑马鱼的繁殖能力[99], 且低剂量暴露产生的内分泌干扰效应, 可经亲子传递对子代产生更显著的影响[100－101]. Yu 等发现暴露于 BDE71 的斑马鱼, 促肾上腺皮质激素释放激素和促甲状腺激素基因的转录水平显著提高[102], 不仅导致血浆 TH 水平升高, 更出现产卵量数十倍的下降[103]. 五氯酚及其副产物六氯苯同时暴露于成年斑马鱼, 可显著提高血浆雌二醇(E2)和睾酮水平, 改变下丘脑-垂体-性腺-肝轴基因表达, 抑制性腺发育, 并可导致生殖障碍[104].

斑马鱼血清 E2 浓度和卵泡发育相关, 通过评估 TCDD 诱导的卵巢相关基因转录的变化发现, TCDD 通过降低促性腺激素的反应性和/或抑制 E2 的生物合成来抑制卵泡成熟, 对雌激素调节信号的干扰也可能是 TCDD 对卵泡发育造成影响的原因之一[105]. 研究表明, PFOS 具有 TH 受体拮抗作用[106], 其暴露可改变下丘脑-垂体-甲状腺(HPT)轴的基因表达, 造成 TH 分泌的紊乱[107]. PFOS 还是雌激素受体(estrogen receptor, ER)激动剂, 干扰类固醇的合成[106], 暴露后雄性和雌性斑马鱼肝脏 VTG 基因表达均显著增加, 调节性激素平衡的基因显著下调[63, 108]. DDE 同样能够使雌性斑马鱼 VTG 的表达增加, 导致成熟卵母细胞数量减少, 但 GSI 无显著变化[109]. Raldua 等采用 T4 免疫荧光定量破坏试验测定甲状腺功能, 确定 DDT 等物质可引起斑马鱼体内 T4 免疫反应性显著降低[110]. 值得注意的是, DDT 与其主要代谢物 DDE 在斑马鱼体内产生的 TH 干扰效应并不相同, 但都引起甲状腺功能受损[111].

另有研究表明, 以 PCB126 暴露于斑马鱼胚胎(24—48 hpf)后, 胰腺发育受到影响, 进而干扰胰岛素的分泌, 增大了暴露个体患糖尿病的风险[112]. 然而, 体型较小的斑马鱼, 为实验操作带来一定困难, 同时这也促使显微操作技术的进一步发展. 近年来, 研究人员已经不再局限于对传统斑马鱼模型的应用, 对其进行适当的基因改造成为学者进一步研究 POPs 内分泌干扰效应的发展趋势[113－114].

2.2　青鳉鱼

青鳉鱼的雌雄易于通过背鳍和臀鳍进行区分, 产卵与光照周期密切相关, 并且在繁殖过程中, 雌鱼产生的卵细胞通过细丝附着于身体, 所以繁殖活跃的雌鱼很容易被识别和观察[26, 115]. 以上特点为观察内分泌紊乱对两性青鳉性腺异常发育、GSI 变化提供方便. 此外, 雌性青鳉只有在雄性的交配行为下才会成功交配和产卵, 生殖行为受促性腺激素释放激素等内分泌物的调控, 便于监测外源化学物通过内分泌毒性效应对生殖行为造成的干扰[64, 116].

PCBs 暴露会扰乱青鳉的内分泌系统，产生的部分毒性作用可通过母体转移至下一代卵中，进而影响子代的发育[117]. 研究发现，PCBs 能够诱导雌性青鳉 VTG 表达，并可抑制绒毛膜蛋白相关基因的表达[118]. 通过对分子水平的进一步研究，监测到暴露后的青鳉鱼体内与内分泌破坏有关的分子标志物的转录显著增加[119]. 作为一种雌激素激动剂，DDT 在性腺分化期能够改变雄性青鳉的性腺发育，促进绒毛膜促性腺激素、VTG 以及 ER 基因的表达，且亲代暴露后繁殖产生的子代更容易受到 DDT 的干扰诱导合成 VTG[120]. 利用实时定量 PCR 技术，有学者监测到暴露于 *p*, *p*'-DDE 的部分青鳉鱼肝脏中 VTG-1、VTG-2、胆囊激素原和 ERα 的基因表达明显增加，并与暴露的 DDE 显示出良好的剂量效应关系的 VTG-1、VTG-2 可作为监测 DDE 的首选生物标志物[77]. 通过卵子显微注射暴露 DDE 后发现，孵化后性腺发育成熟的雄性青鳉睾丸形态正常但偏小，雌性青鳉卵母细胞减少，两性 GSI 均较低[121]. DDT 能够提高青鳉体内 E2 的浓度和 ER 活性，在适当浓度暴露下，*p*, *p*'-DDE 和 *o*, *p*'-DDT 均可诱导雄性青鳉转变为雌雄同体[122].

PBDEs 也被证明能够增加青鳉促性腺激素及其受体和类固醇生成酶的合成[123]. Zhao 等在探索 PBDEs 和多环芳烃对青鳉联合毒性过程中发现，单独暴露于苯并 [a] 芘（BaP）能显著抑制 F1 代胚胎的生殖力和卵蛋白含量，而 BDE47 能够显著消除 BaP 的抑制效果，并推测这种现象可能与 PBDEs 诱导青鳉体内 E2 水平的增加有关[124]. 在对全氟烷基化合物混合物的多代雌激素效应研究时发现，暴露于 PFOS、全氟辛酸（perfluorooctanoic acid, PFOA）等混合物的三代青鳉鱼中，F1 代性别比率显著改变，GSI 下降且孵化率受抑制，而 F2 代个体 VTG 表达诱导明显[125]. Kang 等证明，尽管 PFOS 和 PFOA 在青鳉体内都有 EDCs 的作用且结构相似，但实验发现，两者对卵黄蛋白生成素和胆囊生成素的转录调控不同，即对繁殖作用的抑制方式存在差异[126].

利用青鳉鱼雌雄易分辨的特点，可高效监测受 POPs 内分泌干扰时引起的鱼群性别比例失调、GSI 异常等现象. 在控制光照条件下，可调控青鳉的产卵周期，为进一步研究 POPs 对卵母细胞以及对子代的影响提供更大的自由度. 卵内纳米注射等高新技术的应用，在准确暴露开展实验的同时，将不断开拓青鳉鱼在 POPs 内分泌干扰研究中的应用潜力.

2.3 非洲爪蟾

非洲爪蟾的受精、胚胎发育及变态发育过程均在水环境中发生，其生存容易受到水环境中 POPs 的影响[127－128]. 例如在发育过程中，爪蟾的性别分化及性腺发育极易受到环境中 EDs 的影响，变态反应过程主要由 TH 等激素驱动，使得非洲爪蟾对具有内分泌干扰效应的物质较为敏感[129]. 经过科学研究的反复筛选，非洲爪蟾被确定为研究化学物质内分泌干扰效应和生殖毒性的实验模型之一[78, 130].

PCBs 能够降低非洲爪蟾体内 TH 水平，并可显著改变 T4 转运蛋白、Ⅱ型和Ⅲ型脱碘酶等 3 个具有调节 TH 水平的相关蛋白基因的表达[128]. Qin 等将 PCB3 和 PCB5 暴露于变态期非洲爪蟾，经显微观察发现，实验组雄性非洲爪蟾性腺出现明显异常，包括睾丸结构疏松，生精管、精原细胞和精子减少等，表明 PCB3 和 PCB5 对非洲爪蟾的性腺具有明显的雌性化作用[130]. 李焕婷等的研究结果与此相似，并发现 PBDEs 的暴露能够导致雄性非洲爪蟾睾丸组织中出现早期卵细胞并导致精子排列混乱等雌性化特征[131]. TH 受体和 AhR 信号通路之间存在相互联系，通过对比 T3 和 TCDD 暴露对变态反应的影响，结果发现 TCDD 诱导 AhR 靶细胞细胞色素 P450 1A6 的表达增加 1 000 倍，并使得变态相关基因 *Kruppel* 因子双倍表达，同时导致 T3 效应降低了 40%[132]. 不同浓度 BDE47 暴露于爪蟾蝌蚪后，其大脑中 TH 相关基因的表达下调，进而阻碍了蝌蚪的生长发育[133]. 为探索 DDE 暴露存在的雌激素或抗雄激素效应，Hoffmann 等将雄性非洲爪蟾连续暴露于 DDE 4 个夜晚之后，DDE 同时显示出雌激素和抗雄激素效应，使得非洲爪蟾的性唤起能力降低，生理和生殖行为出现异常[134].

POPs 进入非洲爪蟾体内后，一些酶、蛋白质的合成受到影响，性腺发育以及生殖行为出现异常. 变态发育是评价 POPs 内分泌干扰效应时的重要生理生化过程，POPs 造成的内分泌物质紊乱容易通过变态发育异常表现出来. 深入研究表明，POPs 引起生物体内分泌干扰效应与基因水平的调控有关，需要进一步加大对分子水平开展调查研究的力度.

3　水生模式生物在 POPs 神经行为毒性研究中的应用(Application of aquatic biological models in the study of neurobehavioral of POPs)

POPs 引起的神经毒性在上世纪就得到了广泛关注, 以 PCBs 为例, 有学者对人类神经发育相关的 10 项流行病学中的 PCBs 水平作了对比研究[135－136]. 在孕期接触 POPs 会导致子代注意力的缺乏和长期的学习障碍, 并与学龄前儿童认知能力的低下、智力和运动测试得分不足有关[137－138]. POPs 引起的神经毒性可能会对生物体的行为、应急反应等造成影响, 从而进一步影响生物的生存和繁殖[139－141].

3.1　斑马鱼

以斑马鱼研究 POPs 的神经毒性, 能够同时进行神经毒性效应的鉴别和神经毒物的筛选[142－143]. 在利用斑马鱼建立模型用于监测外源化合物的神经毒性时, 所得数据与哺乳动物相关数据具有较强的相关性, 并能在细胞、分子水平深入探索不同外源化合物的神经毒性机理, 这表明斑马鱼可以作为神经毒性的预测动物模型[144].

研究人员发现, PCB126 可致斑马鱼适应新环境的能力受损[23]. 针对 PCBs 和 BDE47 神经元毒性的研究发现, 两种物质暴露均降低了整个胚胎中的多巴胺含量, 并增加了 3,4-二羟基苯基乙酸/多巴胺比率, 多巴胺能神经元功能受到抑制[145]. 为确定 PCBs 神经毒性效应作用的分子靶点, 研究者将斑马鱼暴露于 Aroclor 1254, 对其基因组的微阵列分析显示, 有 21 个与神经相关的基因表达发生显著变化, 并发现中枢神经系统的结构和生化发生变化[146]; 与此同时发现, 相比于对照组, 实验组斑马鱼自由游泳速度下降, 视觉惊吓试验中的回避位移量减少[147]. 而 BDE71 则通过下调神经元微管蛋白基因的 mRNA 表达, 对神经传递和神经元发育造成影响, 同时引起乙酰胆碱酯酶(AChE)活性显著增加, 机体出现过度活跃[148]. 有证据显示, 亲代暴露于 PBDEs 后, 在 F1 卵中检测到 PBDEs 的残留, 并发现幼鱼体内 AChE 的活性被显著抑制, 中枢神经系统发育的基因表达水平出现显著降低[149]. 有学者对 PBDEs 暴露后的斑马鱼进行学习记忆测试, 并记录相关基因的表达状况, 发现行为改变的同时大脑中的神经相关基因表达也受到影响[150]. Chou 等观察到斑马鱼总游泳距离和活跃时间均与组织中 BDE47 浓度呈负相关[151], 触觉反应敏感性和游泳速度降低, 且仔鱼的神经管和脑室中的脑脊液流动更慢, 推测可能与产生的神经行为毒性有关[50, 152].

TCDD 虽然是典型的致畸污染物, 但通过对发育性神经毒性的分子基础研究发现, TCDD 可显著降低胚胎大脑发育的能力, 导致 168 hpf 幼鱼大脑的神经元总数减少 30%[153]. 在开展 PFOS 的神经行为毒性研究时发现, 不同的生命阶段长期暴露于 PFOS 会对成年斑马鱼的行为和 F1 代的形态、行为和生存产生不利影响[24]. 利用斑马鱼癫痫发作行为模型研究 DDT 对神经发育的交互作用, 发现斑马鱼胚胎在接触 DDT 或 DDE 之后, 对软骨藻酸诱发的癫痫行为更为敏感, 最明显的是出现摇头行为[139]. 斑马鱼的环境适应性、逃逸反应以及神经递质活性、神经元的生长等生理指标在 POPs 暴露后出现一种或多种异常, 造成行为失常的同时也可对其相关基因的表达造成影响, 表明了斑马鱼具有多个毒性监测终点, 可用于 POPs 神经行为毒性的评价.

3.2　青鳉鱼、非洲爪蟾

目前青鳉鱼在评价 POPs 神经行为毒性方面研究较少, 可供参考的文献相对缺乏. 已有研究表明, POPs 能够对青鳉鱼的行为造成影响. 在利用青鳉鱼研究 TBT 和 PCBs 的神经行为毒性时发现, 接触 PCBs 增加了直游和环游的频率, 这表明 PCBs 会导致青鳉过度活跃[154]. 而 Nakayama 等在研究中发现暴露于 PCBs 的青鳉鱼游泳速度以剂量依赖的方式降低[155]. 暴露于 PBDEs 会在小鼠和大鼠发育中引起神经行为毒性, 而对暴露于 PBDEs 的青鳉鱼行为测试结果表明, 胚胎暴露于 BDE71 可能会改变其生命后期的活动量、应急反应、捕食率和学习能力[141]. 关于利用青鳉鱼评价 POPs 的神经行为毒性的实验多停留在观察研究阶段, 且文献多为早期发表, 深入进行机理机制的研究较少. 一方面是由于该领域开展的研究相对不足; 另一方面, 相比于斑马鱼, 在评价 POPs 神经行为毒性过程中, 青鳉鱼具有的突出优势有待发掘.

以非洲爪蟾评价 POPs 的神经行为毒性效应的应用较为深入, 不乏在细胞和分子水平开展的研究. 非二噁英类多氯联苯(non-dioxin-like PCBs, NDL-PCBs)的神经毒性效应以破坏突触前过程(包括钙稳态和神经递质运输)为特征. 在以非洲爪蟾卵母细胞为模型研究 NDL-PCBs 的神经毒性时发现, 不存在神经递质 GABA 的情况下, PCB19、PCB47、PCB51 和 PCB100 可以充当完全激动剂激活突触后

GABA(A) 受体, GABA(A) 受体的增强和激活取决于 NDL-PCBs 的暴露浓度, 其中 PCB47 的激活作用最显著[156－157]. 以不同浓度的 PCBs 对 18 dpf 的蝌蚪进行 2 d 暴露, 表明 PCBs 显著抑制了神经生长因子和 β-肌动蛋白的表达, 且高剂量组蝌蚪出现严重的形态学异常、行为缺陷, 生存率显著下降[158－159]. 为了探索 BDE47 及其代谢物 6-OH-BDE47 是否发挥相似的作用, Hendriks 等研究了 PCB47, BDE47 和 6-OH-BDE47 对非洲爪蟾卵母细胞中 GABA(A)表达的影响, 结果表明, PCB47 和 6-OH-BDE47 能够充当 GABA(A)受体激动剂, 但未观察到 BDE47 对受体产生影响[160]. 通过将哺乳动物脑神经膜微移植到非洲爪蟾卵母细胞的质膜中, 来研究毒物对中枢神经系统离子通道存在的影响, 确定 DDT 在脉冲退极化时引起 TTX 敏感性的内向钠电流的浓度依赖性增加, 并导致了 Na^+通道失活、动力学的减慢, 而 DDE 则没有显著影响[161]. 另外, DDT 的暴露对非洲爪蟾的捕食行为有着显著影响, 出现觅食能力下降[140]. 以非洲爪蟾为模型对 POPs 神经毒性研究不断推进, 学者们对 POPs 毒性作用靶点的定位把握的越来越准确, 有利于从根本上预防和治疗 POPs 引起的神经系统疾病.

4 其它水生生物模型在 POPs 毒理学评价中的应用趋势 (Application trend of other aquatic biological models in toxicological evaluation of POPs)

4.1 稀有鮈鲫

稀有鮈鲫(*Gobiocypris rarus*)属于硬骨鱼纲、鲤形目、鲤科、鮈鲫属, 是一种仅分布于我国四川省大渡河水系的本土鱼种. 体长约 4 cm, 在实验室条件下可实现周年繁殖, 5 d 左右产 1 次卵, 每次产卵上百颗, 作为我国的本土鱼种, 2010 年稀有鮈鲫被我国环境保护部列为新化学物质测试推荐首选的本土试验鱼种[162－163]. 目前国内已有大量学者以稀有鮈鲫为模型, 开展了关于外源化合物的胚胎急性毒性、内分泌干扰效应、生殖毒性、基因毒性等研究[164－167]. Li 等利用稀有鮈鲫对 BDE209 的生殖内分泌毒性进行了评价, 发现暴露浓度达到 10 μg·mL^{-1} 后实验组仔鱼体内Ⅱ型脱碘酶(*dio*2)和碘化钠转运体(*nis*) mRNA 水平显著上调, 成年鱼肝脏中甲状腺激素受体 a(*tra*)、*dio*2 和 *nis* mRNA 水平显著上调, 而大脑中 *dio*2 和 *nis* mRNA 水平则显著下调, 并发现雄性稀有鮈鲫睾丸的精子发生受到抑制[168]. 表 2 列举了国内学者利用稀有鮈鲫研究部分化学物质毒理学效应的实例.

表 2 稀有鮈鲫在外源化合物毒理学研究中的应用

Table 2 Application of *Gobiocypris rarus* in toxicology research of exogenous compounds

暴露物质 Exposed substances	暴露浓度 Exposure concentration	暴露时间 Exposure period	毒性效应 Toxicological effects	文献 References
铜(Cu)、锌(Zn)、镉(Cd)	0.001—1.000 mg·L^{-1}	72 h	发育畸形, 与代谢、发育相关的基因表达发生改变	[169]
铅 (Pb)	—	96 h	肝脏线粒体功能紊乱和结构损伤, 免疫相关基因表达水平显著提高	[170]
Cd^{2+}、三卡因甲磺酸盐、对氯苯胺	≥0.4、3、10 mg·L^{-1}	—	在颜色偏好上由蓝色和绿色转变为黄色和红色	[171]
吡虫啉、硝苯并吡喃、二甲呋喃	0.1、0.5、2 mg·L^{-1}	60 d	造成氧化应激, SOD、CAT活性显著增加, 并出现DNA损伤	[172]
噻虫嗪	0、0.5、5、50 ng·L^{-1}	90 d	肝脏组织学损伤和性腺发育延迟, 对HPG轴基因表达的调控显示出性别差异	[166]
BaP	0、0.1、0.3、1.0、3.0 μg·L^{-1}	28 d	鱼体睾酮和E2的含量变化, 肝脏中VTG基因的表达被显著抑制	[167]
BaP、邻苯二甲酸二酯	0.1、1.0, 10、100 μg·L^{-1}	28 d	睾酮含量升高, 但E2含量下降, 部分基因表达量发生变化	[173]
双酚A	—	63 d	E2和睾酮水平以及卵巢基因组DNA甲基化程度均呈现剂量效应关系	[174]
有机磷系阻燃剂	1.0、10、100 ng·L^{-1}	60 d	Na^+/K^+ ATPase相关基因被显著下调, 精子质量下降	[175]
十溴联苯醚 (BDE209)	0.01、0.1、1.0、10 ng·L^{-1}	21 d	雌鱼的肝脏损伤, 雄鱼睾丸中精子的发生受到抑制	[168]
TBT	1.0、10、100 ng·L^{-1}	60 d	鱼体总脂质、总胆固醇、甘油三酯和脂肪酸的含量显著增加	[176]
环磷酰胺	0.3、0.6、1.2、2.4、9.6 ng·L^{-1}	120 h	外周血红细胞微核和异常率增加, 与环磷酰胺存在浓度-效应和时间-效应关系	[164]
2,4-二氯-6-硝基苯酚	2.0、20、200 μg·L^{-1}	—	死亡率和畸形率增加, 孵化率、体长和体重均降低, 甲状腺激素水平改变	[177]

注: SOD表示Superoxide Dismutase, 超氧化物歧化酶; CAT表示Catalase, 过氧化氢酶; HPG轴表示Hypothalamus-Pituitary-Gonadal axis, 下丘脑-垂体-性腺轴.

经过实验证明, 以稀有鮈鲫为模型进行毒理学研究, 不仅灵敏度高, 而且研究结果具有良好的重复性[165, 178], 在毒理学研究中的应用潜力巨大, 可在国际范围内推广使用

4.2　其它水生生物模型的应用

物种的敏感性差异是影响毒性评价的重要因素, 对 POPs 的毒理评价需要从不同的营养水平选择合适的生物来进行研究[179]. 除了以上介绍的斑马鱼、青鳉鱼等营养层级较高的水生生物, 处于食物链底端的大型蚤等浮游动物在物质循环和能量流动中起着重要作用, 属于水环境中较为重要的初级消费者, 对环境中重金属、POPs 等物质敏感, 对其毒性效应的监测评价能够预防此类物质对营养层级较高生物体的潜在危害[180－182]; 广泛分布于淡水水体的真核生物四膜虫, 培养简单经济、可控性强, 并且科学家已经建立起用于四膜虫相对成熟的分子遗传学操作方法与技术, 可推动其成为研究外源化合物毒理机制的单细胞生物模型[183－184]; 用于水体污染研究的指示生物——霍甫水丝蚓, 是淡水生态系统中重要的底栖生物, 生理结构简单, 实验成本低廉, 灵敏度高, 接触污染物后还会出现自断等异常行为, 能够作为一种有效的生物模型应用于毒理学研究[185－186]. 在表 3 中列出了关于以上几种水生生物模型在环境毒物研究中的实际应用情况, 为将其应用于 POPs 的毒理学效应研究提供参考.

表 3　其它水生生物模型在外源化合物毒理学研究中的应用

Table 3　Application of other aquatic biological models in toxicology research of exogenous compounds

生物模型 Biological models	暴露物质 Exposed substances	主要结论 Conclusions	文献 References
大型蚤	BDE 209	繁殖毒性大于发育毒性, 降解生成的还原中间产物毒性更大	[180]
	化学分散剂Corexit 9 500	表现出慢性生殖毒性, 并阻碍幼蚤生长发育	[187]
	双氯芬酸	与代谢、发育和繁殖相关基因的表达量与暴露剂量和时间呈现依赖性关系	[188]
	PFOA、PFOS	对活动抑制的程度均随暴露时间延长而增强	[181]
	PFOS	总产卵量、体长和内禀增长率均受到显著抑制	[179]
	三氯生(TCS)	新生蚤数量、体长及自然增长率均增大, SOD活性变化	[189]
四膜虫	钩吻碱	抑制生长, 造成氧化应激, 抗氧化酶的表达上调	[190]
	氧化石墨烯	增殖显著受到抑制, 部分出现明显凋亡现象, SOD水平呈先升后降的趋势	[191]
水丝蚓	Cu^{2+}、Hg^{2+}、Pb^{2+}	随着暴露浓度的升高, 水丝蚓体内SOD活性呈先升后降的趋势	[192-194]
	Cd、PFOS	SOD活性、谷胱甘肽水平和丙二醛含量均显著变化	[186]
	Cd	SD活性受抑制, AP活性增加, 消化道上皮细胞线粒体结构损伤	[195]

注: SD表示Succinate Dehydrogenase, 琥珀酸脱氢酶; AP表示Alkaline Phosphatase, 碱性磷酸酶.

5　结语与展望(Conclusion and prospect)

POPs 物质种类繁多, 结构复杂多样, 已经在全球范围内对生态环境造成了污染. 不同环境介质中的 POPs 可通过大气沉降、雨水冲刷、地表径流等多种方式渗入江、河、湖、海, 经食物链传递, 蓄积在各级生物体内并能产生多种毒理学效应. 对 POPs 导致的异常生理现象机制的研究, 可以帮助人类为相关疾病的诊断、治疗和预防提供具有针对性的有效措施. 动物模型可有效解析 POPs 的毒理效应机制, 斑马鱼、青鳉鱼、非洲爪蟾凭借自身优势在 POPs 毒理学评价中逐渐被广泛应用. 斑马鱼和青鳉鱼体型较小, 生理周期短, 胚胎透明且发育速度快, 能够实现在无创条件下的连续观察, 被广泛应用于发育毒理学研究; 通过对其典型生理指标以及相关基因表达的监测、行为的观察, 能够对 POPs 引起的内分泌干扰效应、神经行为毒性进行有效的研究. 非洲爪蟾作为典型的蛙类模式生物, 产卵量大、产卵周期可由人工条件控制, 由蝌蚪到幼蛙的变态发育过程在评价 POPs 的发育毒性及内分泌干扰效应中尤为关键.

水生模式生物在进行 POPs 毒理学评价中具有突出优势, 但同样存在无法忽视的问题. 例如斑马鱼、青鳉鱼体型微小, 在节省成本、提供方便的同时, 也为实验操作带来了困难, 提高了开展实验的操作条件. 其次, 需要加紧对 POPs 在生物体内蓄积、代谢、转化等相关基础研究, 以便为开展 POPs 毒理

学评价提供数据支持. 另外, 需加快推进对转基因、分子生物学技术以及代谢组学的研究应用, 进一步开拓水生模式生物在 POPs 毒理学评价中的应用潜力. 聚焦水生模式生物在 POPs 毒理学研究中的开发应用, 对于 POPs 毒理机制的深入探索、控制生态环境污染、建立相关疾病预测模型具有重要意义.

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