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淡水环境中抗生素抗性基因的来源、归趋和风险

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摘要: 近年来淡水体中抗生素耐药菌及抗生素抗性基因(antibiotic resistance genes, ARGs)的广泛分布和快速传播已成为全球性的环境健康热点问题, 国内外学者围绕淡水环境中 ARGs 的主要来源、多介质分布、转移机制及 ARGs 与微生物群落的互作机制开展了一系列研究。本文综述了医疗废水、污水处理厂尾水和养殖废水作为淡水环境中 ARGs 主要来源的关键作用, 分析了国内外淡水环境中 ARGs 多介质分布和归趋特征, 阐明了淡水环境中 ARGs 传播扩散途径和归趋影响因素, 归纳了 ARGs 风险形成机制与评价方法, 提出了未来关于淡水环境中 ARGs 的研究热点和趋势, 以期 ARGs 环境与健康风险管控提供参考。目前关于 ARGs 产生过程与归趋特性的认识仍相对局限, ARGs 在水生食物链中动态归趋特征、传播扩散过程和暴露风险形成机制的相关研究亟待加强, 淡水环境 ARGs 生态健康风险的系统评估方法也需尽快建立。

关键词: 抗生素抗性基因; 抗生素; 水生生物; 毒理风险机制; 可移动遗传元件

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Source, Fate and Risk of Antibiotic Resistance Genes in Freshwater Environment

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Abstract: In recent years, the widespread distribution and rapid spread of antibiotic-resistant bacteria and antibiotic resistance genes (ARGs) in freshwater bodies has become a global environmental health hotspot. Previous studies have focused on the main sources and multi-media distribution of ARGs, transfer mechanism and the interaction mechanism between ARGs and microbial communities in freshwater environments. This article reviews the key roles of medical wastewater, sewage treatment plant tail water, and aquaculture wastewater as the main sources of ARGs in freshwater environments, analyzes the multi-media distribution and fate of ARGs in freshwater environ-

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ments at a global scale, and clarifies the propagation and diffusion pathways of ARGs in freshwater environments. It summarizes the risk mechanism and risk assessment methods of ARGs, and proposes the research hotspots and trends of ARGs in freshwater environment for future studies, in order to provide reference for management and control of environmental and health risk of ARGs. The understanding of the production process and fate of ARGs is still relatively limited. Research on the dynamic fate characteristics, spreading process and exposure risk formation mechanism of ARGs in the aquatic food chain needs to be strengthened. The systematic assessment method of ARGs ecological health risk in freshwater environment is also needed to be established as soon as possible.

Keywords: antibiotic resistance genes; antibiotics; aquatic organisms; toxicological risk mechanisms; mobile genetic elements

自20世纪40年代青霉素投入临床使用以来,抗生素作为人类和动物体内病原性目标致病菌的致死药物,被广泛应用于医疗临床及畜禽和水产养殖。全球抗生素使用量近15年上升了65%^[1],我国抗生素生产量和使用量全球居首,年均使用量超过15万t^[2]。抗生素的产能过剩、过量使用以及抗生素废水的处理与排放缺乏有效监管,导致大量未被生物体充分吸收和代谢的抗生素随城市尾水、养殖废水等途径直接或间接进入河湖水生生态系统,因此河湖水体中抗生素检出率不断上升^[3]。抗生素的持久性环境残留对环境微生物群落施加进化选择压力,催生了具有多重耐药基因的抗性细菌^[4]。

抗生素抗性基因(antibiotic resistance genes, ARGs)兼具“可自我复制和传播扩散”的生物特性与“不易消亡和环境持久”的物化特征,可在不同细菌间横向转移甚至自我扩增,导致微生物耐药性快速扩散,被认定为一种新型环境污染物^[5]。目前在养殖场废水、污染处理厂、淡水地表水、饮用水、土壤、沉积物和空气等不同环境介质中检测出的ARGs高达50余种^[6]。耐药菌株大量繁殖的后果是抗生素的治疗效能逐渐降低甚至消失,最终导致无药可医。全球每年约70万人死于耐药性病原菌感染,淡水体中抗生素耐药菌及ARGs的广泛分布和快速传播已成为全球性的环境健康热点问题^[7]。本文综述了国内外淡水环境中ARGs主要来源、分布特征、传播扩散途径和风险形成机制的研究进展,归纳了未来一段时期关于淡水环境中ARGs的研究热点和趋势,以期为ARGs环境与健康风险管控提供参考。

1 淡水环境中抗生素及抗性基因的主要来源 (Main source of antibiotics and resistance genes in freshwater environment)

1.1 医疗及制药废水

医疗和制药废水中抗生素的残留浓度较高,易

诱导产生ARGs。人体通过口服或注射服用抗生素后,肠道内会诱导产生耐药菌株。这些耐药菌株随粪便排出体外进入医疗废水,大大增加了医疗废水中耐药抗性菌株和ARGs的检出频率。例如,我国河南省新乡市3家医院废水中*tetO*绝对丰度高达 $(8.34 \pm 1.23) \times 10^7$ copies·mL⁻¹^[8]。*ermB*在北京海淀区某医院医疗废水中的相对丰度高达 2.1×10^{-2} copies·16S-rRNA⁻¹^[9]。国外医疗废水中的ARGs丰度也处于较高水平。例如,罗马尼亚的克鲁日医院废水中磺胺类抗性基因*su1*相对丰度为 $5.33 \times 10^{-2} \sim 1.94 \times 10^{-1}$ copies·16S-rRNA⁻¹, β -内酰胺类抗性基因*bla_{SHV}*的相对丰度为 $1.69 \times 10^{-3} \sim 4.39 \times 10^{-3}$ copies·16S-rRNA⁻¹^[10]。ARGs的高检出率和丰度水平表明医院废水是ARGs污染的主要来源。

医疗废水中以四环素类、大环内酯类、磺胺类、喹诺酮类和 β -内酰胺类抗性基因居多。中国北方医院^[8-9, 11]废水中含有四环素类、大环内酯类、磺胺类、喹诺酮类和 β -内酰胺类ARGs。荷兰医院废水中以大环内酯类(*ermB*、*ermF*)、四环素类(*tetB*、*tetM*)、喹诺酮类(*qnrS*)和 β -内酰胺类(*bla_{OXA}*、*bla_{SHV}*)抗性基因为主^[12]。美国密西根州^[13]、新加坡^[14]、越南^[15]、瑞典^[16]和印度中部^[17]医院废水中检出较高丰度的 β -内酰胺类抗性基因。

抗生素类药品生产过程中排放废水的抗生素残留含量通常较高,选择性诱导ARGs的几率大大增加。中国东南部地区制药废水中检测出*ermB*、*ermC*和*qnrS*等24种抗性基因,其中*ermB*含量高达 $(2.96 \pm 0.88) \times 10^8$ copies·mL⁻¹,*aac*、*aph*次之,绝对丰度分别为 $(1.63 \pm 2.10) \times 10^7$ copies·mL⁻¹和 $(2.22 \pm 2.72) \times 10^7$ copies·mL⁻¹^[18]。中国北方地区制药厂废水中检测出的ARGs绝对丰度范围为 $(1.46 \pm 0.34) \times 10^2 \sim (1.78 \pm 0.51) \times 10^8$ copies·mL⁻¹,其中最终排放废水中*ind1*日负荷高达 $(7.74 \pm 0.92) \times 10^{16}$ copies^[19]。

由此可见,制药废水中 ARGs 含量也处于较高水平,已成为水环境中 ARGs 的潜在储存库。

医疗和制药废水一般要经过自带的污水系统处理后才能排放到外界,但废水处理仍含有较高水平的 ARGs。例如,我国辽宁省制药废水处理系统可以有效去除四环素类抗性细菌,但是会使磺胺类抗性细菌浓度上升(5.01×10^4 CFU·mL⁻¹)^[20];乌鲁木齐医院污水处理系统可去除 0.86 ~ 1.81 个数量级的细菌,但处理后的水中仍然含有浓度为 1.01×10^8 ~ 1.39×10^8 CFU·mL⁻¹ 的抗生素抗性细菌(antibiotic resistance bacteria, ARBs)^[21]。欧洲医院自带的污水处理系统仅能将 ARGs 的相对丰度降低 1 ~ 3 个数量级,而 *tetA*、*bla_{SHV}* 和 *suI* 只能略微去除^[10]。由此可见,处理后的医院和制药废水依然含有一定水平的 ARGs,排入淡水环境中可能导致 ARGs 进一步传播扩散。

1.2 污水处理厂尾水

污水处理厂尾水中微生物群落结构复杂,残留的抗生素处于亚抑菌浓度级别(指小于最低抑菌浓度的抗菌药物浓度,可在不影响细菌生长的前提下对细菌耐药性、致病性等生理学特性产生影响^[22]),已成为 ARGs 在抗生素选择性压力下发生横向转移进而传播扩散的理想场所,尾水中 ARGs 丰度水平通常处于较高水平。我国江西省北部某地区污水处理厂尾水中氨基糖苷类、 β -内酰胺类、磺胺类和四环素类等 9 种类型 ARGs 均有检出,其中氨基糖苷类抗性基因相对丰度最高,平均丰度达到 0.32 copies·16S-rRNA⁻¹^[23]。波兰中部 13 个污水处理厂均检出基因 *bla_{TEM}*,平均丰度为 10^3 ~ 10^4 copies·mL⁻¹^[24]。韩国大光州地区 2 个大型污水处理厂尾水中 ARGs 日负荷高达 4.2×10^{18} copies,其中一个污水处理厂尾水中磺胺类抗性基因和 β -内酰胺类抗性基因水平最高,日负荷分别为 2.1×10^{18} copies 和 1.5×10^{18} copies^[25]。

传统污水处理工艺中没有针对 ARGs 的去除流程,而膜反应器、高级氧化等一些新型污水处理技术虽然对污水中的 ARGs 有一定的去除效果,但无法实现完全去除^[24]。例如,氯消毒工艺可使 ARGs 减少 2.98 ~ 3.24 个数量级,紫外线照射使 ARGs 降低 2.48 ~ 2.74 个数量级^[26];膜生物反应器可以使四环素抗性基因丰度(*tetA*、*tetM* 和 *tetW*)分别下降了 0.88、3.47 和 2.51 个数量级^[27]。氯消毒、紫外照射和膜生物反应器的去除机制主要基于 ARGs 从废水向污泥、生物膜或沉积物的迁移,而不是从环境中清除^[28]。高级氧化工艺和双金属系统可以有效灭活甚

至杀死 ARBs,达到真正意义上的环境清除,但氧化剂的去除效果容易受到废水中腐殖质、碳水化合物和脂肪酸等有机物的影响^[29-30]。Fenton 氧化技术对 *suI*、*tetX*、*tetG* 和 *int1* 的去除率可分别达到 3.98、3.80、2.57 和 4.62 个数量级;UV/H₂O₂ 氧化技术可使尾水中 ARGs 丰度减少 2.8 ~ 3.5 个数量级^[31]。*mFe/nCu* 双金属系统可以有效杀灭 ARBs 和 ARGs, DNA 去除效率高达 57%,*tetA*、*tetE*、*tetQ*、*ermB*、*suI* 和 *int1* 的 DNA 分别可以去除 2.69、2.31、2.18、2.97、2.08 和 2.76 个数量级^[32]。

污水处理厂尾水中的 ARGs 排放到淡水环境后往往导致受纳水体 ARGs 丰度大幅上升,污水处理厂尾水已成为淡水环境中 ARGs 的重要来源。我国四川地区污水处理厂上游检出 *suI* 5.40×10^4 copies·mL⁻¹、*int1* 4.03×10^5 copies·mL⁻¹ 以及其他基因(*qnrS*、*tetX*、*bla_{TEM}* 和 *ermB*) 10^2 ~ 10^3 copies·mL⁻¹,污水处理厂尾水入河后下游水体 *tetX*、*bla_{TEM}*、*ermB* 和 *int1* 的相对丰度分别高出 1.46 ~ 3.51 倍^[33];海河流域子牙河系某支流接受污水处理厂尾水后,四环素类抗性基因 *tetA* 绝对丰度由 1.93×10^4 copies·L⁻¹ 增加到 1.26×10^7 copies·L⁻¹,磺胺类抗性基因 *suI* 和 *suI* 的绝对丰度分别从 2.85×10^6 copies·L⁻¹ 和 9.18×10^7 copies·L⁻¹ 增加到 1.59×10^6 copies·L⁻¹ 和 8.40×10^6 copies·L⁻¹^[34]。

1.3 养殖废水

近年来兽用抗生素在养殖业广泛使用,致使畜禽和渔业养殖废水成为淡水环境中 ARGs 的重要储存库。我国北京和江西两地的养殖废水中检出较高丰度的四环素类抗性基因(*tetM*、*tetX*)和大环内酯类抗性基因(*ermB*、*ermF* 和 *ermA*),绝对丰度分别为 $(6.91 \sim 24.3) \times 10^{10}$ copies·mL⁻¹ 和 $(7.16 \sim 14.5) \times 10^{10}$ copies·mL⁻¹^[35];西北地区最大的鲟鱼养殖内陆湖瀛湖中检出 8 类共 59 种 ARGs,养殖水域 ARGs 相对丰度为 5.59×10^{-6} ~ 2.30×10^{-2} copies·16S-rRNA⁻¹,远高于上游非养殖型水域^[36];江苏省 12 个畜牧场废水中检出 5 类 22 种 ARGs,其中 *tetM*、*suI*、*suI* 和 *acrB* 检出率为 100%,*tetG*、*tetW*、*tetC*、*ermB*、*aph*、*qnrD* 和 *acrA* 检出率高于 90%^[37]。越南隆安虾类养殖区分离菌株中 *suI*、*suI*、*qnrA* 和 *ermB* 检出率分别达到 94.1%、82.4%、88.2% 和 94.1%^[38]。

养殖废水中四环素类、磺胺类及喹诺酮类抗性基因检出率最高,与该类抗生素在养殖业的大量使用密切相关^[39]。我国珠三角鸭鱼混养塘中磺胺类抗

性基因(*su11* 和 *su12*)所占比例超过 50%^[40];杭州湾河口的水产养殖区磺胺类抗性基因 *su11* 丰度最高,喹诺酮类抗性基因 *qnrS* 次之,相对丰度分别为 $9.97 \times 10^{-3} \text{ copies} \cdot 16\text{S-rRNA}^{-1}$ 和 $1.94 \times 10^{-2} \text{ copies} \cdot 16\text{S-rRNA}^{-1}$ ^[41]。但是,养殖场的净水设施并不能完全去除 ARGs。我国武汉市养猪场废水净化后,ARGs 丰度仍高达 $3.1 \times 10^4 \sim 7.1 \times 10^8 \text{ copies} \cdot \text{L}^{-1}$,其中 4% ~ 57% 持续存在于下游小溪和邻近土壤中^[42];江苏省金坛市养殖废水处理,总 ARG 的相对丰度降低了 84%,厌氧消化、初级沉淀和人工湿地有助于去除 ARGs,但次级沉淀则增加了 ARGs 总含量^[43]。

1.4 源解析与通量估算

淡水环境中 ARGs 污染来源复杂(图 1),准确判断 ARGs 的排放通量并解析其负荷来源,可以为遏制 ARGs 环境污染和规避生态风险提供理论基础。Duarte 等^[44]整合大量文献中抗生素和 ARGs 数据,使用线性混合模型描述两者整体关系,并根据不同抗生素特定的耐药性选择效应校正浓度系数,建立了一个抗生素选择潜力聚合风险度量模型,可根据抗生素压力和环境隔室的类型预测 ARGs 的总体丰度变化。另一方面,ARGs 的来源解析面临许多挑

战,来自本地遗传成分的干扰、其他污染物的选择作用和 ARGs 调查的不全面都会使 ARGs 追踪发生偏差^[45]。crAssphage 是一种最近发现的 DNA 噬菌体,已用于追踪人类粪便 ARGs 污染对河流沉积物中 ARGs 的影响^[46-47],并证实河流沉积物中 ARGs 很大程度受到人类粪便污染程度的影响(50% ~ 63.7%)^[48-49]。Chen 等^[48]结合快速期望最大化的微生物源跟踪方法(fast expectation-maximization microbial source tracking, FEAST)与线性判别效应分析方法(linear discriminant analysis effect size method, LEfSe),基于高通量测序的宏基因组和 crAssphage 噬菌体分析,建立了淡水环境中 ARGs 来源解析方法,发现白洋淀 80% 以上的 ARGs 负荷来自府河。Chen 等^[49]使用微生物来源分析工具 SourceTracker 和 crAssphage 噬菌体,结合 ARGs 和微生物分类的宏基因组特征,系统厘清了 ARGs 的源汇关系,量化了不同污染来源对河流沉积物中 ARGs 的潜在贡献,证实了污水处理厂尾水贡献了河流沉积物中 81.6% ~ 92.1% 的 ARGs 和 49.3% ~ 68.1% 的微生物。总体而言,宏基因组学是构建 ARGs 源追踪方法框架的核心,对 ARGs 源解析具有深远意义^[45]。

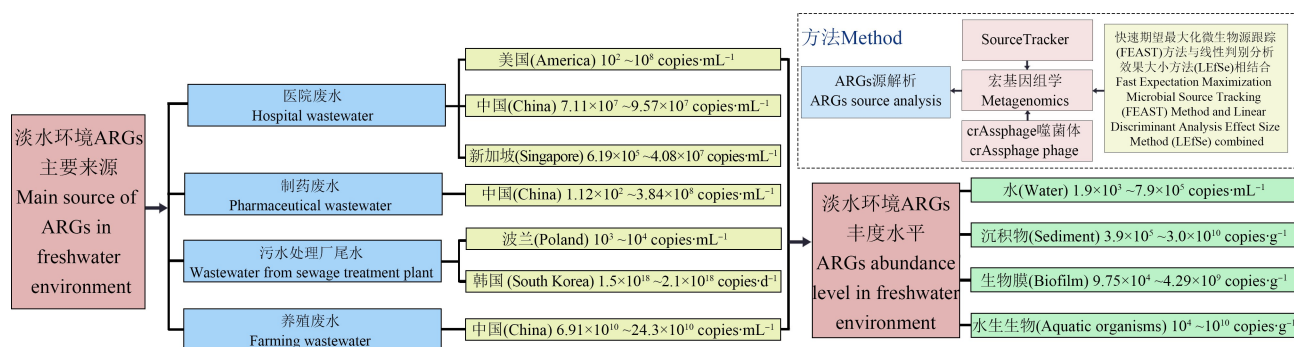


图1 淡水环境中抗生素抗性基因 (ARGs) 的赋存特征、主要源通量与源解析方法

Fig. 1 Occurrence characteristics, main source fluxes and source analysis methods of antibiotic resistance genes (ARGs) in freshwater environment

2 淡水环境中抗生素抗性基因多介质分布和归趋特征 (Multimedia distribution and fate characteristics of antibiotic resistance genes in freshwater environment)

近年来 ARGs 在淡水不同环境介质中被广泛检出(图 2),检出率最高的是四环素类抗性基因和磺胺类抗性基因。国内外典型河流和湖泊的 ARGs 丰度水平如表 1 和表 2 所示。我国北江河中磺胺类 ARGs 含量最高的是 *su11* 和 *su12*(平均值分别为 1.41

$\times 10^{-2} \text{ copies} \cdot 16\text{S-rRNA}^{-1}$ 和 $1.58 \times 10^{-3} \text{ copies} \cdot 16\text{S-rRNA}^{-1}$),四环素类 ARGs 中 *tetC* 的相对丰度最高 ($8.30 \times 10^{-2} \sim 13.20 \text{ copies} \cdot 16\text{S-rRNA}^{-1}$)^[50]。我国海河流域中磺胺类抗性基因 *su11* 是优势 ARGs,丰度高达 $6.4 \times 10^9 \text{ copies} \cdot \text{mL}^{-1}$ ^[51];海河流域子牙河支流检出含量最高的 ARGs 为四环素类抗性基因和磺胺类抗性基因,其中 *tetA* 和 *tetB* 抗性基因的绝对丰度范围是 $1.93 \times 10^4 \sim 1.26 \times 10^7 \text{ copies} \cdot \text{L}^{-1}$ 和 $2.22 \times 10^4 \sim 9.96 \times 10^4 \text{ copies} \cdot \text{L}^{-1}$,*su11* 和 *su12* 抗性基因的绝对

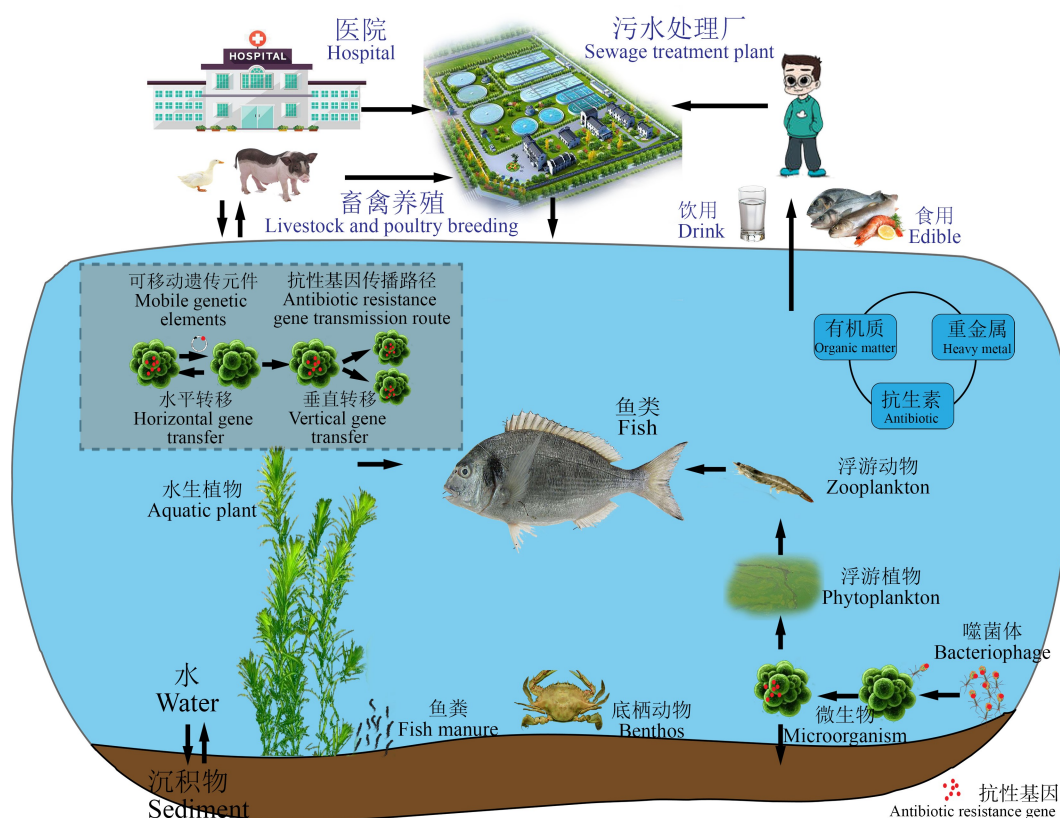


图2 淡水环境中抗生素抗性基因的主要来源和传播扩散路径

Fig. 2 The main source and spread of antibiotic resistance genes in freshwater environment

丰度是 $2.85 \times 10^6 \sim 9.18 \times 10^7 \text{ copies} \cdot \text{L}^{-1}$ 和 $1.59 \times 10^6 \sim 8.40 \times 10^6 \text{ copies} \cdot \text{L}^{-1}$ [34]。我国西安巴河检出 23 种不同类别的 ARGs, 其中 *tetC* 是四环素类抗性基因中相对丰度最高的 ARGs ($6.50 \times 10^{-3} \sim 4.50 \times 10^{-1} \text{ copies} \cdot 16\text{S-rRNA}^{-1}$) [52]。我国太湖 *su1* 的检出率为 100%, 其丰度范围为 $1.9 \times 10^3 \sim 7.9 \times 10^5 \text{ copies} \cdot \text{mL}^{-1}$ [53]。淡水环境已成为 ARGs 潜在的富集库和释放源。

国内淡水 ARGs 丰度水平整体高于国外, 与抗生素水平、人类活动强度和开发程度有关 [3, 54-55]。在我国, 海河、珠江和长江下游人类活动强度高、抗生素使用量大, 抗生素排放强度位居全国前 3 位 [54]。长三角 80% 儿童尿液中检出兽用抗生素, 水源水、饮用水厂、自来水管网及饮用水系统末端中广泛检出 ARGs, 抗生素和 ARGs 污染问题及其引起的健康风险较为突出 [56]。相对于河流, 湖泊的水体交换能力较弱、换水周期更长, 具有更大的潜力来储存和积累 ARGs, 抗生素及 ARGs 的停留时间增加并在湖泊内缓慢循环; 另一方面, 湖泊水产养殖更为普遍, 投放的饵料中含有大量抗生素, 导致 ARGs 表达

水平上升 [3, 57]。长江下游太湖、洪泽湖等浅水湖泊畜禽渔业养殖发达, 抗生素水环境赋存量高, 导致湖泊中 ARGs 丰度水平普遍高于河流 [58-59]。

淡水沉积物中 ARGs 丰度普遍高于上覆水。在我国, 西安巴河 ARGs 最高丰度为 $5.49 \times 10^6 \text{ copies} \cdot \text{mL}^{-1}$, 而沉积物中 ARGs 丰度高达 $4.38 \times 10^7 \text{ copies} \cdot \text{g}^{-1}$ [52]; 长江口沉积物中 *su1* 绝对丰度为 $3.29 \times 10^5 \sim 2.04 \times 10^6 \text{ copies} \cdot \text{g}^{-1}$, 比上覆水 ($2.26 \times 10^4 \sim 3.19 \times 10^5 \text{ copies} \cdot \text{mL}^{-1}$) 高出 1 个数量级; 沉积物中的 *acc(6')-Ib* 基因丰度范围为 $2.51 \times 10^6 \sim 6.37 \times 10^6 \text{ copies} \cdot \text{g}^{-1}$, 而在水样中的丰度范围 $2.68 \times 10^4 \sim 3.05 \times 10^4 \text{ copies} \cdot \text{mL}^{-1}$ [60]; 太湖地表水和沉积物样品中所有 ARGs 的丰度范围分别为 $4.8 \times 10^5 \sim 1.5 \times 10^8 \text{ copies} \cdot \text{mL}^{-1}$ 和 $5.4 \times 10^6 \sim 3.0 \times 10^{10} \text{ copies} \cdot \text{g}^{-1}$ [53]。

关于地下水中 ARGs 污染的报道相对较少, 但已逐渐引起关注。在我国, 深圳茅洲河地下水中检出 127 种 ARGs 和 10 种可移动遗传元件, 其中 116 种 ARGs 与地表水检出种类一致, 主要与地表污水入渗有关 [61]; 洪湖地下水含有 27 种 ARGs, 其中 *qnrB*、*qnrS* 和 *tetQ* 含量均高于地表水 [62]; 厦门东南

表 1 国内外典型河流水中抗生素抗性基因 (ARGs) 丰度

Table 1 The antibiotic resistance genes (ARGs) abundance of typical rivers at home and abroad

河流 River	国家 Country	年份 Year	<i>suII</i>	<i>suI2</i>	<i>tetA</i>	<i>tetB</i>	<i>tetC</i>	<i>tetW</i>	<i>tefO</i>	<i>tnpA-03</i>	<i>blaCTX-M</i>	参考文献 References
长江中游	中国	2015	2.2×10^{-1}	9.7×10^{-3}	1.04×10^{-2}	—	—	(1.61 ~ 4.67) $\times 10^5$	(1.43 ~ 5.05) $\times 10^5$	—	—	[67]
Middle reaches of the Yangtze River	China											
珠江	中国	2011	6.0×10^5	3.0×10^5	—	—	—	—	—	—	—	[68]
Pearl River	China											
海河	中国	2013—2014	6.4×10^9	—	—	—	—	—	—	—	—	[51]
Haihe River	China											
辽河	中国	2014	9.0×10^2	8.6×10^2	—	—	—	—	—	—	—	[69]
Liaohe River	China											
黄河	中国	—	—	—	—	—	—	—	—	1.07×10^4	—	[70]
Yellow River	China											
黄浦江	中国	2011	(0.32 ~ $1.15) \times 10^5$	(0.43 ~ $4.19) \times 10^5$	(0.22 ~ $3.66) \times 10^3$	(2.53 ~ $4.65) \times 10^1$	(0.52 ~ $4.55) \times 10^3$	(1.61 ~ $4.67) \times 10^5$	(1.43 ~ $5.05) \times 10^5$	—	—	[71]
Huangpu River	China											
子牙河	中国	—	(0.285 ~ $9.18) \times 10^7$	(1.59 ~ $8.40) \times 10^6$	1.93×10^1 ~ 1.26×10^4	(2.22 ~ $9.96) \times 10^1$	—	—	—	—	—	[34]
Ziya River	China											
北江(相对丰度)	中国	2009	1.41×10^{-2}	1.58×10^{-3}	—	—	8.30×10^{-2} ~13.20	—	—	—	—	[50]
Beijing River (Relative abundance)	China											
巴河(相对丰度)	中国	2017	—	—	—	—	(0.0065 ~ $4.50) \times 10^{-1}$	—	—	—	—	[52]
Ba River (Relative abundance)	China											
泰晤士河	英国	—	6×10^4	1×10^5	—	—	—	3×10^3	—	—	—	[72]
River Thames	UK											
莱茵河	德国	2011—2012	—	—	—	—	—	—	—	—	2.01×10^2	[73]
Rhine River	Germany											
密西西比河	美国	2011—2014	8.2×10^5	—	—	—	—	3.4×10^4	—	—	—	[74]
Mississippi River	USA											
恒河	印度	2012	—	—	—	—	—	$1.64 \sim 6.43$	—	—	—	[75]
Ganges River	India											
塞纳河	比利时	2016	(1.6 ~ $3.5) \times 10^{-2}$	(0.21 ~ $1.83) \times 10^{-1}$	—	—	—	(0.43 ~ $2.76) \times 10^{-1}$	9.2×10^{-2}	—	—	[76]
Seine River	Belgium											

注:—表示文章中没有相关数据;表中标明相对丰度的单位为 $\text{copies} \cdot 16\text{S-rRNA}^{-1}$,其余均为 $\text{copies} \cdot \text{mL}^{-1}$ 。
Note: — indicates that there is no relevant data in the article; the unit of relative abundance indicated in the table is $\text{copies} \cdot 16\text{S-rRNA}^{-1}$, and the rest are $\text{copies} \cdot \text{mL}^{-1}$.

部垃圾填埋场地下水中检测出 171 种 ARGs 和 8 种可移动遗传元件(mobile genetic elements, MGEs), ARGs 绝对丰度范围为 $2.5 \times 10^9 \sim 1.27 \times 10^{11}$ copies $\cdot$ L $^{-1}$, 其中多抗基因及 β -内酰胺类、四环素类抗性基因含量最高^[63]。罗日尼亚地下水中检出 *bla*_{SHV}、*floR*、*sulI* 和 *tetA* 等 11 种 ARGs, 其相对丰度为 $6.61 \times 10^{-7} \sim 2.30 \times 10^{-1}$ copies $\cdot$ 16S-rRNA $^{-1}$, 其中四环素类抗性基因(*tetC*、*tetO* 和 *tetW*)遵循了环境污染的规律, 可将这组基因作为探寻人类影响的环境示踪剂^[64]。

生物膜是淡水环境中 ARGs 的重要载体。西班牙托德拉河流域生物膜中含有的 *sulI* 和 *ermB* 相对丰度分别为 10^{-2} copies $\cdot$ 16S-rRNA $^{-1}$ 和 10^{-3} copies $\cdot$ 16S-rRNA $^{-1}$ ^[65], 加泰罗尼亚周边河流生物膜样本中检测出高丰度的 *sulI* ($10^{-2.5}$ copies $\cdot$ 16S-rRNA $^{-1}$)、*suI2* ($10^{-3.2}$ copies $\cdot$ 16S-rRNA $^{-1}$)、*ermB* ($10^{-2.9}$ copies $\cdot$ 16S-rRNA $^{-1}$)、*tetW* ($10^{-3.7}$ copies $\cdot$ 16S-rRNA $^{-1}$) 和 *tetO* ($10^{-3.3}$ copies $\cdot$ 16S-rRNA $^{-1}$)^[66]。中国长江中游生物膜样品中 *intI1*、*sulI*、*suI2*、*aac(6')-Ib*、*tetA*、*tetQ* 和 *tetW* 等 7 种抗性基因的检出率为 100%, 磺胺类抗性基因中 *sulI* 丰度最高(范围为 $3.20 \times 10^7 \sim 2.50 \times 10^{11}$ copies $\cdot$ g $^{-1}$)、*suI2* 次之(平均丰度为 5.94×10^8 copies $\cdot$ g $^{-1}$); 喹诺酮类抗性基因中 *acc(6')-Ib* 和 *qnrS*

绝对丰度最高(范围为 $9.75 \times 10^4 \sim 7.44 \times 10^7$ copies $\cdot$ g $^{-1}$ 和 $7.28 \times 10^6 \sim 2.52 \times 10^9$ copies $\cdot$ g $^{-1}$); 四环素类抗性基因 *tetA* 丰度范围为 $2.68 \times 10^5 \sim 4.29 \times 10^9$ copies $\cdot$ g $^{-1}$, 大环内酯类抗性基因 *ermB* 的最高丰度为 1.50×10^7 copies $\cdot$ g $^{-1}$ ^[60]。

淡水生态系统中的各类水生生物也是 ARGs 的重要载体。细菌和噬菌体间的相互作用促进了 ARGs 在它们之间的水平转移^[81]。淡水细菌和浮游动物间的互作对 ARGs 转移具有正面影响, 例如水蚤相关的细菌群是 *tetA* 的潜在载体, 而这些细菌的生物膜结构可能促进 ARGs 水平转移^[82]。葡萄牙地表水分离出的蓝藻菌株中检出 *strA-strB*、*sulI* 和 *intI1* 这 3 种 ARGs, 且这些菌株对抗生素敏感性较低, 这是蓝藻可能从环境中获得耐药性并传播到其他微生物的有力证据^[83]。细菌、噬菌体甚至是胞外 DNA 都可吸附在水生生物表面或消化道中, 水生动物粪便将 ARGs 释放到水环境中使其进一步传播扩散^[3, 57]。ARBs 被鱼摄入后与肠道细菌接触, ARGs 经质粒介导在体内发生转移并随细菌增殖, 将近 15% 的肠道细菌含有编码抗性基因的质粒, 鱼粪中 ARBs 是摄入数量的 8 倍; 斑马鱼后肠 ARBs 浓度几乎是前肠的 25 倍, 转导结合体总数超过 10^8 CFU, 已成为促进 ARGs 传播的重要区域^[84]。

表 2 国内外典型湖泊 ARGs 丰度

Table 2 ARGs abundance of typical lakes at home and abroad

湖泊 Lake	国家 Country	环境相 Environmental facies	年份 Year	<i>sulI</i>	<i>suI2</i>	<i>tetW</i>	<i>tetC</i>	参考文献 References
太湖 Taihu Lake	中国 China	水相 Water phase	2015—2017	$1.9 \times 10^3 \sim 7.9 \times 10^5$	—	—	—	[53]
巢湖 Chao Lake	中国 China	沉积相 Sedimentary facies	2013	$1.2 \times 10^6 \sim 6.9 \times 10^8$	$1.18 \times 10^6 \sim 6.9 \times 10^8$	—	—	[77]
洪泽湖 Hongze Lake	中国 China	沉积相 Sedimentary facies	2013	—	—	—	9.77×10^6	[78]
洞庭湖 Dongting Lake	中国 China	沉积相 Sedimentary facies	—	4.23×10^6	6.59×10^6	—	—	[3]
湖泊群 Lake group	瑞士 Swiss	水相 Water phase	2011	2.97×10^{-2}	—	2.2×10^{-5}	—	[57]
的的喀喀湖 Lake Titicaca	秘鲁 Peru	水相 Water phase	2014	$10^{-3} \sim 5 \times 10^{-3}$	$5 \times 10^{-4} \sim 10^{-3}$	—	—	[79]
瓜伊巴湖 Lake Rio Guaíba	巴西 Brazil	水相 Water phase	2016—2018	1.5×10^2	—	—	—	[80]

注: —表示文章中没有相关数据; 水相浓度单位为 copies $\cdot$ mL $^{-1}$, 沉积相浓度单位为 copies $\cdot$ g $^{-1}$ 。

Note: — indicates that there is no relevant data in the article; the unit of water phase concentration is copies $\cdot$ mL $^{-1}$, and the unit of sedimentary facies concentration is copies $\cdot$ g $^{-1}$.

3 影响抗生素抗性基因水环境归趋的主要环境因子(Main environmental factors affecting the fate of antibiotic resistance genes in water environment)

整合子、转座子及质粒等 MGEs 是 ARGs 水平转移的重要载体,其水平转移是促进 ARGs 传播扩散的主要机制^[85]。密歇根湖沉积物中发现与质粒相关的 ARGs 占已鉴定总数的 32% ~ 100%^[86]。漳溪河中除万古霉素抗性基因外的 ARGs 总丰度与 MGEs 呈显著正相关($P < 0.01$)^[87]。

菌落结构对 ARGs 水平转移影响显著。Zheng 等^[87]发现变形细菌(Proteobacteria)的氢藻(*Hydrogenophaga*)和拟杆菌属(*Bacteroidetes*)的小球藻(*Prevotella*)与 ARGs 呈显著正相关($P < 0.05$)。Reddy 和 Dubey^[88]发现美国 Cuyahoga 河中 ARGs 丰度与细菌群落组成密切相关,方差分解分析(variance partitioning analysis, VPA)表明细菌群落间的相互作用可解释 80.7% 的 ARGs 丰度变化。印度恒河水中 ARGs 与杆菌、拟杆菌、甲烷杆菌、假单胞菌、副细菌和酸性细菌显著相关^[89]。

温度是影响 ARGs 及其载体存活的重要因素,在一定程度上影响 ARGs 的丰度水平和传播扩散过程。加拿大 Sumas 河流域的四环素类 ARGs 丰度与温度呈正相关($P < 0.05$),细菌浓度在降雨量较少且温度较高的夏季较低,而 ARGs 丰度却保持较高水平^[90]。春季我国宁波市某城郊河道 ARGs 绝对丰度显著低于其他季节(12% ~ 36%),而夏季 ARGs 绝对丰度最高(2.81×10^9 copies · mL⁻¹),表明温度升高可能导致 ARGs 传播扩散;16S rRNA 基因与 ARGs 之间的显著相关性表明温度也是驱动 ARGs 基因转移的潜在因素^[87]。

水环境中 ARGs 丰度水平与人类活动强度关系密切。我国宁波市水库、森林附近河流中的 ARGs 丰度与农田、城镇附近河流中的 ARGs 丰度存在显著差异,农田附近河流样品中 ARGs 的绝对丰度比水库和森林附近河流高 3.47 倍 ~ 5.58 倍,而下游城镇人类活动强度相对较高,附近河流 ARGs 水平最高^[87]。我国北江中 ARGs 数量和多样性主要与污水处理厂、水产养殖场和牲畜废水等污染源相关,中游地区的人口密度和污染源少于上游和下游地区,ARGs 丰度也相对较低^[91]。

淡水环境中重金属、有机物等其他污染物也会影响 ARGs 的丰度水平。我国北江沿岸的 *tetW* 和重金属可能存在关联^[91]。印度恒河中 ARGs 丰度与

重金属抗性基因(metal resistance genes, MRGs)丰度呈显著正相关($P < 0.05$),这可能源于重金属的选择性压力或 ARGs 与 MRGs 之间的共变,但这种稳定相关性表明河流系统中可能发生了 ARGs 和 MRGs 的共选过程^[88]。我国温瑞塘河中总有机碳(total organic carbon, TOC)、溶解性总氮(total dissolved nitrogen, TDN)与 ARGs 绝对丰度呈正相关,与氨基糖苷类、 β -内酰胺类、大环内酯-林可酰胺-链阳菌素 B (MLSB)和四环素类 ARGs 丰度的相关性更强($P < 0.01$)^[92]。我国湖州市染色废水中孔雀石绿、苯乙烯等 6 种有机化合物促进 RP4 质粒共轭转移,转移效率最高超过空白对照组 219 倍^[93]。

4 淡水环境中抗生素抗性基因的传播扩散途径(Transmission and diffusion of antibiotic resistance genes in freshwater environment)

尽管淡水地表水环境中抗生素的赋存水平维持在微克或纳克级,但低浓度抗生素的长期暴露不可避免地会通过基因突变诱导、水平传递和代际遗传的方式促使细菌耐药性产生和扩散。ARGs 可通过接合、转化和传导等多种方式进行水平基因转移(horizontal gene transfer, HGT)^[94],水平转移可使非亲生物之间进行遗传物质共享,被认为是 ARGs 传播的主要机制^[95]。整合子、转座子及质粒等 MGEs 在水相和沉积物相中对 ARGs 传播的贡献最大^[96]。质粒是多种 ARGs 的携带载体,可通过供体菌和受体菌借助抗性菌毛相互连接形成的通道进行传播^[97]。DNA 和质粒也可在游离状态下被感受态或者开放损伤诱导系统的细菌接受^[98],从而完成 ARGs 在同属或不同属细菌间的转移^[99]。噬菌体也可帮助 ARGs 进行水平转移^[100],在侵蚀细菌的同时获得 ARGs,在产生新的噬菌体-细菌裂解-释放新噬菌体-侵蚀新细菌的循环中积累扩散,噬菌体的蛋白外壳使其在胞外环境中具有更高的持久性,在 ARGs 水平转移过程中扮演重要角色^[101]。

ARGs 另一个传播途径是垂直转移(vertical gene transfer, VGT),指携带 ARGs 的菌株通过自我繁殖将 ARGs 传给子代的过程。自然水环境中有些微生物自带对抗生素具有抗性的基因序列,这些基因序列可以通过繁殖垂直传给下一代,使子代也对抗生素具有抗性,而这种 ARGs 就能在代际增殖过程中继续传播^[102]。VGT 还有另一种模式,即在发生水平基因转移的情况下,受体与原始供体结合后形成的转导结合物通过继发性 HGT 和细胞共同生

长,并进一步促进 ARGs 传播。转导结合体从获得的 ARGs 中发展出新的性状,成为 ARGs 通过 VGT 传播的主要驱动力^[100]。

5 淡水环境中抗生素抗性基因风险形成机制与评价方法 (Risk formation mechanism and evaluation method of antibiotic resistance gene in freshwater environment)

淡水环境中的 ARBs 和 ARGs 无法被降解、稀释等自然过程完全去除,且 ARBs 一般不会通过微生物降解或紫外降解失活,即使失活后其含有 ARGs 的游离 DNA 仍保持完整并将 ARGs 传递给非抗性菌株^[103]。自然淡水体中病原性 ARGs 转移是罕见且随机的事件,但病原体仍可能会因为与抗生素抗性菌株接触足够长时间而发生 HGT^[104]。ARGs 通过饮水、食用水产品和农产品等途径进入人体系统后会在肠道菌群内部转移^[103],促使细菌尤其是致病菌的耐药性进一步增加,导致抗生素治疗效能逐渐降低甚至消失^[105]。因此,建立完善 ARGs 生态健康风险评估体系显得尤为重要。

学术界已提出包括危害识别、危害评估、暴露评估和风险评估的抗生素耐药性风险评估框架^[106-107],但微生物功能群落和 ARGs 之间的关系^[106]、传播途径中 ARBs 数量以及各种健康后果仍不明确^[108]。如何减少这些不确定性对风险评估最终结果的影响,是 ARGs 风险评估方法亟待解决的问题。Ashbolt 等^[108]提出了基于最小选择性浓度(minimum selective concentration, MSC)的 ARBs 发生阈值评估方法,基于问题表述(危害、风险设置和途径)、危害暴露评估(ARBs 和 ARGs)、剂量-反应关系等评估病原体致病风险,通过这种病原体风险评估(microbial risk assessment, MRA)定性或定量地评估病原体暴露水平及其对人类健康的后续风险,但体外数据库和计算毒理学研究是 ARGs 风险评估不确定性最小化的关键因素。因此,淡水环境 ARGs 转移扩散的分子生物学调控机制、风险形成过程和人体暴露评估是建立 ARGs 风险评估体系需要突破的关键问题。

6 结论与展望 (Conclusions and prospects)

开展 ARGs 在水生态系统中的多介质环境行为与生物安全研究,阐明其在淡水环境中的源汇机制和生物生态效应,对 ARGs 环境与健康风险管控、淡水饮用水安全保障和水生态系统健康修复具有重要的理论意义和实践价值。国内外学者围绕淡水环境中 ARGs 的主要来源、多介质分布、转移机制及抗生

素抗性与微生物群落的互作机制开展了一系列研究,但目前相关研究工作仍处于初期发展阶段,关于 ARGs 产生过程与归趋特性的认识仍相对局限。建议后期加强关于 ARGs 在水生食物链中动态归趋特征、传播扩散过程和暴露风险形成机制的研究,尽快建立淡水环境 ARGs 生态健康风险的系统评估方法。

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