

DOI:10.7524/j.issn.0254-6108.2024032203

王芳, 赖玮毅, 汪海林. 卤代苯醌类消毒副产物的毒理学研究进展[J]. 环境化学, 2024, 43(7): 2206-2213.

WANG Fang, LAI Weiyi, WANG Hailin. Research progress on toxicology of haloquinoid disinfection byproducts[J]. Environmental Chemistry, 2024, 43 (7): 2206-2213.

卤代苯醌类消毒副产物的毒理学研究进展*

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摘要 卤代苯醌 (halobenzoquinones, HBQs) 是近年来在水体中发现的一类具有潜在毒理学效应且未受管控的新型消毒副产物 (disinfection by-products, DBPs)。本文综述了 HBQs 的化学特征与生成机制、环境中的分布情况, 并对其引起的细胞毒性、氧化应激毒性、遗传毒性、生物毒性进行了概述。这些内容旨在为深入探讨 HBQs 的毒理学机制和全面评估其暴露所可能导致的健康风险及癌症风险提供科学依据。

关键词 卤代苯醌, 消毒副产物, 环境暴露, 毒性评估。

中图分类号 X-1; O6 **文献标识码** A

Research progress on toxicology of haloquinoid disinfection byproducts

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Abstract Halobenzoquinones (HBQs) are newly identified, unregulated disinfection by-products (DBPs) with potential toxicity, recently found in various water bodies. This article reviews the chemical properties, and formation mechanisms of HBQs, as well as their environmental distribution. It provides an extensive overview of the toxicological impacts of HBQs exposure, including cytotoxicity, oxidative stress toxicity, genetic toxicity, and other biological effects. The goal is to offer a scientific basis for further investigation into the toxicological mechanisms of HBQs and to enhance understanding of the potential health risks associated with HBQs exposure.

Keywords halobenzoquinones, disinfection by products, environmental exposure, toxicity assessment.

2024 年 3 月 22 日收稿 (Received: March 22, 2024).

* 国家自然科学基金-重点项目 (22234008), 国家自然科学基金-国家重大科研仪器研制项目 (21927807), 国家自然科学基金-创新研究群体项目 (22021003) 和国家自然科学基金-面上项目 (22274166) 资助。

Supported by the State Key Program of National Natural Science Foundation of China (22234008), National Natural Science Foundation of China - National Major Research Instrument Development Project (21927807), National Natural Science Foundation of China - Innovative Research Group Project (22021003) and General Program of National Natural Science Foundation of China (22274166).

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水是人类生存与社会发展的基础. 饮用水, 作为直接供给人体饮用的水源, 其质量与公众健康密切相关. 为保证饮用水安全, 通常需要向水中添加消毒剂以杀死水中的病原菌. 常用消毒剂如氯气或氯胺等可能与水中的有机物或污染物发生反应并产生消毒副产物^[1]. 卤代苯醌是近年来水体中发现的一类未受管控且具有潜在毒理学效应的新型 DBPs^[2-7]. 虽然其在各类水体中浓度约为 $\text{ng}\cdot\text{L}^{-1}$ 级别^[8], 但相比于已受到美国环境保护署、欧洲联盟理事会及世界卫生组织管控的 DBPs, HBQs 表现出更高的细胞毒性和遗传毒性^[9-12]. 有研究表明长期饮用氯化消毒后的饮用水可能增加患膀胱癌的风险^[13]. 此外, 定量结构毒性关系分析预测 HBQs 是潜在的膀胱癌致癌物质^[14]. 因此, HBQs 可能会对人类健康及生态环境的安全构成威胁. 本文重点关注 HBQs 的化学特征与形成机制、环境污染分布及毒性作用.

1 HBQs 的化学特征与形成(The chemical characteristics and formation of HBQs)

HBQs 的结构基础是苯醌(benzoquinone, BQ), 其环上带有卤素、烷基或羟基修饰(图 1). 这类化合物含有高极性的羰基, 与芳香醌类化合物相似. HBQs 的化学性质与 BQ 密切相关, 尤其在氧化还原和加成反应方面^[15]. BQ 得电子还原为半醌自由基和氢醌(hydroquinone, HQ)^[16], 也可与氧亲核试剂发生氧化反应生成醌环氧化物^[17], 在水溶液中形成多个与 HBQs 结构类似的氧化还原态.

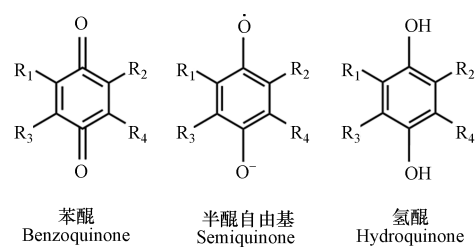


图 1 苯醌、半醌自由基和氢醌的结构

Fig.1 Structure of benzoquinone, semiquinone and hydroquinone

HBQs 并非自然界中存在的天然有机物, 其形成需要水中特定的化合物与消毒剂发生反应. 这些化合物包括游离芳香族氨基酸^[18]、苯醌类似物^[19-20]、芳香型天然有机物^[3]及藻类^[21-22]等. 几种常见的 HBQs 如图 2 所示.

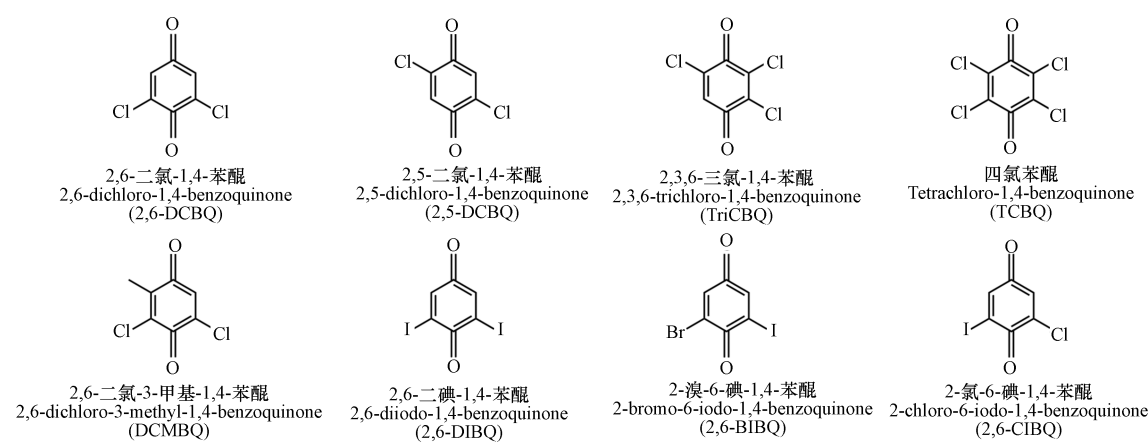


图 2 几种常见 HBQs 结构

Fig.2 Several common HBQs structures

2 HBQs 的环境污染现状(The current status of environmental pollution by HBQs)

HBQs 广泛存在于氯消毒处理的水体中. 自 2010 年首次在加拿大饮用水中检出以来^[4,5], 目前世界多地的饮用水中均检出了 HBQs. 例如, 2012 年美国^[23]和加拿大^[23]9 个饮用水处理厂的 16 份水样本中检出了多种 HBQs, 包括 2,6-DCBQ、2,6-DBBQ、TriCBQ 和 DCMBQ. 其中 2,6-DCBQ 的检出浓度为 $4.5\text{--}274.5\text{ ng}\cdot\text{L}^{-1}$ 且检出率高达 100%, DCMBQ 和 TriCBQ 的检出率分别为 37.5% 和 18.8%. 2015 年日本的 12 座水厂水样^[24]中也发现了 2,6-DCBQ, 检出率为 87.5%, 检出浓度为 $8.0\text{--}51.0\text{ ng}\cdot\text{L}^{-1}$.

近年来,我国多地饮用水体中也检测出 HBQs: 2021 年天津^[25] 水处理厂和相关配水网络中检出 2,6-DCBQ, 采样点 2,6-DCBQ 的浓度随着与饮用水处理厂距离的增加而逐渐降低; 2020 年南京和上海^[9] 不同地区的饮用水中首次检测出了 3 种新型碘化 HBQs(2,6-CIBQ、2,6-BIBQ 和 2,6-DIBQ), 碘化 HBQs 比常见的氯化 HBQs(如 2,6-DCBQ)具有更强的细胞毒性, 因此含有碘化 HBQs 的饮用水可能对人体健康产生更大的威胁^[26]. 此外, HBQs 也在茶水中检出, 且其检出浓度与茶叶的发酵程度呈现正相关性. 这可能与饮用水或茶叶的发酵工艺相关, 茶叶发酵过程中的过氧化物酶和多酚氧化酶会与植物中无机氯与酚基发生反应可能会导致 HBQs 生成^[27].

除饮用水外, HBQs 也存在于经氯消毒处理的游泳池用水中. 经氯消毒的泳池水中 2,6-DCBQ 的浓度在 19—299 ng·L⁻¹ 之间, 较未经消毒的自来水浓度(1—6 ng·L⁻¹)提高了 100 倍^[28]. 中国南宁^[5] 7 个公共游泳池中的 2,6-DCBQ 检出率为 100%, 浓度范围为 4.56—45.30 ng·L⁻¹. 游泳池中的氯代苯醌浓度高于自来水, 这与加拿大的研究结果一致. 与仅通过氯化消毒产生 HBQs 的饮用水不同, 泳池水的化学暴露环境更为复杂. 例如, 游泳者所用的化妆品(如防晒霜和乳液等^[6])中可能含有 HBQs 的前体化合物, 在水中和其他化合物发生反应形成 HBQs.

3 HBQs 的毒理学研究进展(Advances in toxicological research of HBQs)

HBQs 在水体中广泛分布, 虽浓度较低但具有较高的潜在毒性. 近年来, 针对卤代苯醌及其健康风险的研究广泛展开, 通过流行病学研究和实验室研究, 评估不同水平的卤代苯醌暴露对生命体的影响. HBQs 已被发现在细胞毒性、氧化应激毒性、遗传毒性、对水生生物的毒性等多方面表现出毒性效应.

3.1 HBQs 的细胞毒性

细胞毒性是指物质或因素对细胞产生有害的作用, 可能导致细胞损伤或死亡. 基于细胞的环境污染物体外毒性检测已成为评估化合物毒性的一种重要手段, 该方法可快速鉴定和识别具有潜在健康风险的新型污染物. 通过测量化合物的半致死浓度(IC₅₀)可以对化学物质的毒性进行评估. HBQs 已被发现具有细胞毒性, 在以人膀胱癌上皮 T24 细胞为毒性测试对象的研究中, 4 种 HBQs(2,6-DCBQ、2,6-DBBQ、DCMBQ 和 TCBQ)的 IC₅₀ 值在微摩尔水平(1.9—95.6 μmol·L⁻¹), 其中饮用水中最常见的 2,6-DCBQ 对 T24 的毒性最强, 这提示 HBQs 可能对人体泌尿系统有潜在危害. 而已受到管控的 DBPs(N-亚硝基二甲胺、N-亚硝基二苯胺、N-亚硝基吡咯烷等)^[29] 对 T24 细胞的 IC₅₀ 值在毫摩尔水平(4.7—15.0 mmol·L⁻¹), 说明 HBQs 对 T24 细胞的潜在毒性远高于 DBPs. 为保障公众健康, 应采取措施将饮用水中 2,6-DCBQ 等 HBQs 的浓度控制在安全范围内. 此外, 四种 HBQs(2,6-DCBQ、2,6-DBBQ、DCMBQ 和 TCBQ)暴露中国仓鼠卵巢细胞 CHO^[30] 得到的 IC₅₀ 也在微摩尔水平(15.9—72.9 μmol·L⁻¹), 而已受到管控的 DBPs(三卤甲烷、卤乙酸)对 CHO 细胞的 IC₅₀ 在毫摩尔水平(3.96—11.5 mmol·L⁻¹)^[29]. HBQs 对 CHO 细胞的毒性比传统的 DBPs 高出 1000 倍, 上述研究证明 HBQs 具有较高的细胞毒性并可能对人体健康造成更严重的影响.

3.2 HBQs 诱导的氧化应激

活性氧自由基(reactive oxygen species, ROS)引起的氧化应激是醌毒性作用机制之一^[31]. HBQs 中的半醌和羟基自由基结构会导致 ROS 的产生, 引发细胞内氧化应激, 进而对细胞造成氧化应激损伤^[32]. HBQs 还可以消耗细胞内谷胱甘肽(glutathione, GSH), 影响细胞抗氧化酶系统, 加剧氧化应激反应, 导致细胞蛋白质和 DNA 损伤^[11, 33]. 在 T24 细胞中, HBQs 以浓度依赖的方式产生 ROS, 并对 DNA 和蛋白造成氧化损伤, 而抗氧化剂可显著降低 HBQs 对 T24 细胞的毒性作用, 表明 ROS 在 HBQs 诱导的细胞毒性中发挥重要作用^[30]. 同时, HBQs 以浓度依赖性的方式引起细胞 GSH 消耗和细胞谷胱甘肽 S-转移酶活性的增加, 质谱分析证实在水溶液和 HepG2 细胞中 HBQs 与 GSH 可直接反应^[32, 34], 形成多种谷胱甘肽基偶联物(HBQ-SG), 因此 GSH 的减少可能与其氧化或与 HBQs 结合有关^[35]. 此外, HBQs 可以显著改变尿路上皮细胞(SV-HUC-1)氧化应激相关信号通路的信号转导, 从而影响细胞的功能和病理过程^[36]. HBQs 诱导的氧化应激也体现于活体水平. 例如, HBQs 暴露会导致斑马鱼幼鱼体内 ROS 增加, 超氧化物歧化酶活性降低, GSH 含量减少, 以及脂质过氧化水平和脂肪酸代谢异常. 而抗氧化剂可显著减轻 HBQs 诱导产生的影响, 这些结果进一步证实了氧化应激介导 HBQs 毒性的结论^[36-37].

3.3 遗传毒性

遗传毒性是指化学物质或其他外部因素对生物体细胞的遗传物质造成损害或突变的能力。这些改变可能直接或间接影响遗传信息, 从而影响个体健康及后代的遗传稳定性。已有证据表明 HBQs 能够诱导突变, 具有遗传毒性作用。

3.3.1 致突变性

HBQs 能够直接或间接作用于细胞 DNA, 导致细胞遗传信息的改变。HBQs 是反应性亲电物质, 可诱导显著的遗传毒性: 与 DNA 形成加合物^[38], 阻断 DNA 聚合酶活性, 诱导缺失突变、特定位点突变或序列特异性突变等^[39]。毒理基因组学分析显示, HBQs 干扰人膀胱上皮细胞 SV-HUC-1 的 DNA 修复途径, 主要影响碱基切除修复、核苷酸切除修复和同源重组修复^[40]。在经过 TCBQ 处理的 HeLaS3 细胞中检出 DNA 加合物二氯苯醌核苷($\text{Cl}_2\text{BQ-dG}$)^[41-42]。在 SupF 报告基因突变试验中, HBQs 诱导 GC 碱基对上的单碱基替换, 主要是 GC→TA 翻转和 GC→AT 突变^[43]。此外, 如果 HBQs 与关键基因形成 DNA 加合物则可能发生致癌突变。

3.3.2 DNA 氧化损伤

HBQs 诱导的 DNA 氧化损伤可能导致 DNA 结构和功能的异常, 增加细胞突变或发生癌症等风险。DNA 氧化损伤主要表现为细胞 DNA 链断裂、8-羟基脱氧鸟苷(8-hydroxy-2deoxyguanosine, 8-OHdG)和脱嘌呤/脱嘧啶位点(apurinic/apyrimidinic sites, AP sites)的显著增加等。HBQs 诱导 T24 细胞的基因组 DNA 中产生 8-OHdG, 且 DCMBQ 诱导生成的 8-OHdG 水平高于 2,6-DCBQ、2,6-DBBQ 和 TCBQ^[30]; HBQs 也会引起哺乳动物 CHO 卵巢细胞中 p53 蛋白和 8-OHdG 的表达升高^[44], p53 作为肿瘤抑制蛋白, 在协调细胞对基因毒性应激的反应中起着至关重要的作用^[45]。体内实验证明 HBQs 会导致斑马鱼幼鱼体内 8-OHdG 水平升高、DNA 片段化并诱导凋亡相关基因表达变化^[37]。在 HBQs 处理的 HepG2 细胞中检出了 $\gamma\text{-H2AX}$, 表明 HBQs 诱发 DNA 双链断裂, 而 ROS 清除剂的预处理显著抑制了这种情况, 说明 HBQs 可能通过 ROS 介导 DNA 氧化损伤导致 HepG2 细胞的遗传毒性^[46]。在 TCHQ 处理的 HeLaS3 细胞中观察到 AP 位点的形成^[47], 说明 HBQs 可能干扰正常的 DNA 修复机制, 导致遗传信息改变进而引发疾病。因此, 减少甚至避免 HBQs 的暴露是降低 DNA 氧化损伤风险的重要措施。

3.3.3 染色体损伤

外部因素(如辐射、化学物质和病毒等)或内部因素(如氧化应激、DNA 复制错误等)可能导致生物染色体结构或功能上的损害。这些损伤可能影响细胞的正常功能、代谢和生长, 最终导致细胞死亡、突变, 甚至引发癌症^[48]。微核检测(micronucleus assay)通过测量染色体丢失和染色体断裂来评估染色体损伤程度, 可用于评估个体暴露于环境致癌物质和诱变剂的遗传风险^[49]。HBQs 暴露显著增加 HepG2 细胞中的微核频率, 表明 HBQs 可能导致染色体断裂^[46]。HBQs 可诱导人类细胞系膀胱癌 5637 细胞、结肠癌 Caco-2 细胞和胃癌 MGC-803 细胞染色体损伤, 导致微核显著增加, 其中 DCMBQ 对所有测试细胞系的细胞毒性和遗传毒性最高, TCBQ 对所有测试细胞系的毒性最低^[50]。

3.3.4 DNA 甲基化损伤

DNA 5-甲基胞嘧啶(5-Methylcytosine, 5mC)甲基化是哺乳动物中一种主要的表观遗传学标记^[51]。TET 双加氧酶(Ten-Eleven-Translocation enzymes)能催化 5mC 氧化生成 5-羟甲基胞嘧啶(5-hydroxymethylcytosine, 5hmC), 介导 DNA 的主动去甲基化^[52], 这一过程对于调控 DNA 甲基化水平至关重要。HBQs 的暴露会导致细胞内游离亚铁离子含量的升高, 而亚铁离子是 TET 酶的辅助因子之一^[53], 增加的亚铁离子可以提高 TET 酶的催化活性, 从而促进 5hmC 的形成。5mC 向 5hmC 的转换不仅与表观遗传的重编程紧密相关, 而且对于 DNA 的动态去甲基化和组织特异性基因表达的调控也具有重要意义^[54-55]。异常 5hmC 水平可能干扰细胞内正常的 DNA 甲基化模式, HBQs 诱导多基因的去甲基化^[56], 这些基因涉及蛋白质代谢、细胞凋亡、细胞定位与运输以及 RNA 的加工处理等多个关键生物进程^[57, 58]。此外, 癌细胞通常呈现出全基因组的低甲基化^[59], 若 DNA 去甲基化介导癌基因激活, 还可能促进肿瘤发生^[60]。因此, HBQs 可能改变表观遗传修饰水平而具有潜在的致癌性。

3.4 HBQs 对水生生物的毒性

HBQs 广泛存在于水环境中, 因此评估 HBQs 对水生生物的毒性至关重要。斑马鱼作为研究毒性效

应的首选水生生物模型,被广泛应用于研究 HBQs 对水生动物的毒性,这包括斑马鱼在发育过程中受到的损害、心脏和血管系统的不良影响、神经系统的损伤以及因氧化应激和代谢异常导致的毒性作用等。

水生生物的正常生长发育离不开健康的水环境,但是水体中 HBQs 会对斑马鱼造成发育毒性。2,5-DCBQ 影响斑马鱼早期胚胎的正常发育,造成外胚层发育的延迟甚至死亡^[61]; HBQs 的处理会导致斑马鱼幼鱼出现明显的发育畸形,如体长缩短、鱼鳔充气失败、心脏畸形和脊柱弯曲等^[37],其中鱼鳔充气失败可能会导致运动和摄入受限,最终导致死亡率增加^[62]。此外,2,6-DCBQ 暴露可能导致雌性斑马鱼青春期延迟、卵巢生长迟缓和生育能力低下,并可能通过破坏 17- β 雌二醇水平诱导雌性斑马鱼生殖损伤^[63]。且暴露于饮用水消毒副产物或可增加女性卵巢储备功能下降的风险,降低女性生育能力^[64]。

流行病学研究表明,饮用水中消毒副产物含量的增加与心脏先天性缺陷的风险相关。研究发现,孕妇早期接触高水平的 DBPs 增加新生儿出现先天性心脏缺陷的风险^[65]。斑马鱼发育过程的透明以及与人类相似的心血管系统使其成为研究 HBQs 心血管毒性的理想模型。2,6-DCBQ 暴露导致斑马鱼胚胎心房—心室变形、心包水肿、腹部及主干血管变形和血流量减少。这些心脏与血管的畸形可能直接影响心脏泵血功能及正常的输血输氧,导致心跳异常和循环衰竭甚至死亡。此外,心脏特异性标记基因 *myl7* 的表达受到抑制,该基因对心肌细胞的分化和运动至关重要,也证明了 HBQs 对心脏发育的潜在风险^[37, 66]。

HBQs 影响人神经干细胞正常的细胞周期,进而阻碍细胞增殖与分化^[67],表明 HBQs 具有潜在神经毒性^[68]。HBQs 对斑马鱼神经毒性的影响主要表现为运动神经毒性和视觉神经毒性^[69, 70]。经 HBQs 处理过的幼鱼(120 hpf)运动行为能力显著低于正常组,并且神经递质含量降低、神经调节相关基因下调,表明 HBQs 具有运动神经毒性^[37]; HBQs 暴露导致视网膜特定功能相关的多晶体蛋白和角蛋白水平增加,提示 HBQs 具有视觉神经毒性效应^[71]。

HBQs 还引起斑马鱼代谢水平的变化。经 2,5-DCBQ 处理的斑马鱼胚胎表现出代谢异常,且这种异常与暴露浓度呈现正相关性。生物信息分析显示其代谢通路(嘌呤代谢、氨酰-tRNA 生物合成等)发生显著改变^[61]。2,6-DCBQ 显著改变斑马鱼胚胎中的脂质过氧化水平和脂肪酸代谢^[37]。HBQs 可能对斑马鱼的代谢功能产生明显的毒性影响,进而影响其正常的生命活动。

4 总结与展望(Conclusion and prospect)

饮用水消毒副产物 HBQs 存在于氯消毒的饮用水和游泳池水体中,是近年来备受关注的一类新型污染物。通过了解 HBQs 的结构特征和形成机制,可以更好地评估其潜在毒性和环境行为,为相关监管和控制提供科学依据。研究 HBQs 的毒性效应及机理将有助于评估其对人体和环境的风险水平,从而制定相关的安全措施和监管政策,以降低该类化合物对人体和环境的潜在风险。为了保障公众健康和环境安全,需要加强对 HBQs 的毒理学研究,包括生物累积和生物放大效应、环境污染物相互作用机理和影响、人类健康风险评估等。此外,尽管自来水中 DBPs(二氯乙酸和三氯乙酸)已被证明具有内分泌干扰物效应^[72],但 HBQs 是否也具有类似效应,影响人体内分泌系统和生殖、发育等过程,目前的研究仍然不足。因此,HBQs 的毒理研究仍然需要进行深入、全面的探索和研究,以确定其对人体健康的潜在风险,这项工作将是未来的长期任务。

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