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2012—2021 年中国地下水抗生素污染现状及分析技术研究进展

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摘要: 抗生素作为一种新污染物,在不同环境介质中均有检出。未被人类或动物完全吸收和代谢的抗生素会通过废水和废弃物以原型或代谢产物的形式进入环境,并在土壤中积累或淋滤进入地下水。抗生素进入环境可能影响微生物生态,产生抗性基因,甚至威胁人体健康,而地下水作为重要的饮用水源,其抗生素污染问题不容忽视。本文从抗生素的危害、使用情况、污染来源、污染现状、定性定量检测方法的优缺点及适应范围和形态分析及环境效应等方面对近十年来(2012—2021)中国地下水中抗生素的研究现状进行总结。经调查,中国常用 28 种抗生素检出浓度在 0.1~1000ng/L 以上,检出频率较高的抗生素为诺氟沙星、氧氟沙星、磺胺甲恶唑、恩诺沙星、磺胺嘧啶、红霉素等。从空间分布来看,对地下水中抗生素的研究主要集中在华北、西南地区,而对西北地区中地下水抗生素研究程度较低。目前为止受到分析方法检出限及检出种类的限制,对地下水中抗生素的调查及评价还不够全面。通过综述抗生素定性定量分析方法,发现 HPLC-MS/MS 法因其具有灵敏度高、选择性好和定性定量准确的优点是目前应用最广泛的抗生素定量分析方法,而且可利用该方法对环境中抗生素类型进行初步识别,针对主要类型开展定量分析或长期监测,为抗生素环境效应研究提供数据支撑。而当抗生素以不同的带电形态、络合形态、吸附形态存在时,因其理化性质不同会影响测定的准确性、环境行为和毒理学效应,因而开展抗生素的形态分析对进一步准确测定抗生素和评估其环境效应具有重要意义。本文认为,优化定性定量检测方法、分析抗生素的不同形态、全面调查地下水中抗生素和科学评价抗生素形态与生态毒理学效应的关系,是今后地下水中抗生素污染研究的重点课题。

关键词: 地下水; 抗生素; 污染现状; 环境行为; 形态分析; HPLC-MS/MS

要点:

(1) 中国地下水中常检出的 28 种抗生素的浓度变化超过 4 个数量级。

(2) HPLC-MS/MS 法可以对地下水中的抗生素进行准确的定性定量分析。

(3) 抗生素的存在形态影响前处理的回收率、定性和定量结果的准确性。

中图分类号: X502; O657.63 **文献标识码**: A

自 1928 年青霉素问世以来,因其较好的疗效和较高的应用价值,抗生素的生产量和使用量逐年提高,中国作为世界上抗生素生产和使用大国, 2013 年生产量就已达到 24.8 万吨,总使用量约 16.2 万吨[1]。大部分用于人类或动物的抗生素不能被完全吸收和代谢[2],会通过废水和废弃物以原型或代谢产物的形式进入环境[3],并在土壤中积累或淋滤进入地下水[4]。地下水污染相较于地表水具有隐

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蔽性、滞后性和难以逆转性,因此作为饮用水主要水源的地下水中抗生素的污染问题备受关注。

地下水中的抗生素存在威胁人类身体健康和地下水生态系统的风险,完善、成熟和精准的分析方法是地下水中抗生素调查、评价和研究的基础,是抗生素类新污染物防治的技术支撑。作为准确评价地下水中抗生素污染水平的重要基础[5],抗生素分析方法已经从简单的目视比色法发展成利用精密仪器进行高精度定性和定量的检测方法。液相色谱-串联质谱法因具有高灵敏度、高准确度、高选择性等特点,是目前最常用的抗生素定量检测方法[6],该方法在土壤[7]、地表水[8]、地下水[9]、沉积物[10]等环境介质中均有应用;与定量方法相比,液相色谱-串联质谱法由于缺少商业化的定性谱库,只能根据离子碎片判断抗生素的类别,因而高通量的抗生素定性识别仍面临较大的挑战。抗生素的存在形态不仅与其环境效应密切相关,而且影响分析方法的建立,当前有必要对抗生素存在形态与前处理回收率、定性和定量结果准确性之间的关系进行系统研究。

到目前为止,中国对于抗生素的研究仍以地表水和土壤为主,对地下水中抗生素污染问题关注较少[11]。只有在对中国地下水抗生素污染作出全面调查的情况下,才能更有针对地提出解决措施,降低抗生素所带来的风险。本文收集了 2012—2021 年有关地下水中抗生素的相关文献,从抗生素的危害、中国抗生素使用情况、污染现状、定性定量检测方法适应范围和形态分析及环境效应等方面,对近十年来中国地下水中抗生素的检出种类和浓度进行总结,为后续环境研究和科学管理提供依据。

1　环境中抗生素的危害及来源

1.1　抗生素的危害

抗生素(Antibiotics)是指由微生物(如细菌、真菌)等生物所产生的具有抗病原体或其他活性的有机化合物,亦或是由人工合成或半合成的类似物,主要用于治疗和预防细菌及微生物感染所致的人畜疾病,也可以用作生长促进剂刺激养殖动物生长[12]。抗生素按照其结构特点主要分为磺胺类(SAs)、四环素类(TCs)、β-内酰胺类(β-lactams)、喹诺酮类(QNs)、大环内酯类(MLs)、氯霉素类(CPs)、林可霉素(LIN)及其他类抗生素等[13]。各类抗生素的代表物、结构特点及抗菌机理可参照文献[14]。抗生素在不同领域得到了广泛的应用,但因目前的污水处理工艺对于抗生素的去除效率较低,使得抗生素不断地被释放到环境中,造成“假持续”释放现象[15]。

抗生素的选择压力会使细菌产生抗生素抗性基因(Antibiotic Resistance Genes,ARGs),抗性基因的存在使得敏感菌对某种抗生素产生抗性,加剧临床上细菌感染治疗的难度[16]。近年来,抗生素的抗性基因作为一类新的环境污染物[17],受到了国内外研究者的广泛关注[18],在不同的环境介质如水体、沉积物、水生生物等均有 ARGs 检出[19],而抗生素抗性基因的扩散和传播,已经开始威胁到全球人群的健康[20],其危害往往比抗生素本身所带来的环境危害更大。

抗生素进入环境后,会干扰生态系统的物质循环过程,改变微生物群落结构[21],降低微生物群落的多样性[22],影响动植物的生长,从而威胁到生态系统的稳定性、多样性[23]。除此之外,抗生素也会影响微生物的硝化作用、反硝化作用[24]、氨化作用[25]等生态过程。Li 等[26]对中国七大主要河流进行抗生素污染评估发现,海河、黄河中的抗生素污染给无脊椎动物和藻类带来了较高的风险。

除了诱导细菌产生抗性基因,残留在不同环境介质中的抗生素也可能通过多种途径进入人体,对人体健康有潜在风险。饮用水源[27]、食品[28]等介质中有一定的抗生素残留,虽然痕量水平的抗生素不会产生危害,但人类持续摄入,不间断地暴露于环境中所残留的抗生素,会使健康受到威胁。例如β-内酰胺类抗生素代谢物会引起过敏[29],部分抗生素会引起肠功能紊乱等疾病[30]。全球抗生素抗药性(AMR)导致的死亡率为大约每年 70 万人次,预计到 2050 年将增加到每年 1000 万人次[31]。

1.2　中国抗生素使用情况

中国是全球最大的抗生素生产国和消费国[3]。据统计,2013 年中国 36 种常用抗生素的使用总量为 9.27 万吨,大约有 5.40 万吨抗生素被人类和动物排出体外,最终有 5.38 万吨抗生素通过各种废水处理进入水环境[1]。中国药物总用量中抗生素占比为 30%~40%,远远超过其他各类药物所占比例,而欧美等发达国家的比例仅在 10%左右[25]。2020 年中国使用的全部抗菌药总量为 32776.30 吨,使用量排名前三位分别为:四环素类、磺胺类及增效剂、β-内酰胺类及抑制剂[32]。

1.3　地下水环境中抗生素来源

抗生素的大量生产和使用,使抗生素及其代谢产物通过直接或间接的方式进入地表水或土壤,最

终通过淋洗或下渗的方式汇集到地下水中。地下水中抗生素的主要来源途径分为生产来源、使用来源及排放来源等。

制药工厂生产过程中的抗生素随废水、废渣排放进入环境中。河北省某家接受药厂废水的污水处理厂的出水中土霉素的含量高达 19.50mg/L,比城市生活污水土霉素的浓度高出 4~6 个数量级[33]。雷雨洋等[34]对江浙地区各种环境介质中的抗生素残留状况进行统计,发现江浙地区制药废水中的抗生素浓度高达 5.70mg/L,因污水处理厂处理效率低,某些抗生素经处理后浓度仍高达 88μg/L。

按使用来源将抗生素分为人用和兽用。人用抗生素主要用于治疗疾病;兽用抗生素主要应用于农业、畜牧业及水产养殖,用于控制动物传染病和促进动物生长[35]。抗生素用于动物体后,只有一小部分抗生素会被动物吸收,30%~90%的抗生素都将通过粪便排泄到环境中[36],一旦粪便作为有机肥料施入农田[37],则抗生素通过淋洗、下渗作用进入地下水。Zhou 等[38]对中国典型养殖场抗生素的排泄量进行了调查,发现附近的井水、小溪和农田中均检出多种抗生素。除此之外,抗生素还会通过病人排泄物排出、丢弃的过期抗生素药物、残留在医疗器械上的抗生素等方式进入环境中[39],最终到达地下水。

工厂生产抗生素所产生的废水、畜牧业及农业所产生的废水及人类产生的生活污水、医疗废水都通过污水收集系统,进入污水处理厂。因目前中国对于废水中抗生素处理技术尚不完善,处理工艺未涉及抗生素去除[37],使得抗生素通过淋滤、地表径流等进入地表水和地下水中。除直接排入环境水体的抗生素外,经过处理的废水通过地表水回灌[40]、再生水补给[41]等方式进入地下水。

抗生素会通过不同的途径排放到环境中并且到达地下水体[42],在地下水中蓄积,影响微生物生态、产生抗性基因,甚至威胁人体健康,所以地下水抗生素污染问题不容忽视。抗生素在地下水中的污染来源与迁移途径如图 1 所示。

2　中国地下水抗生素污染现状

中国作为抗生素生产和使用大国,消费量是英国的 150 倍,人均使用量是美国的 10 倍[43],是欧洲国家的 6~10 倍[44]。而直到 2005 年,中国才开始逐渐关注抗生素污染问题,相较于瑞典、美国、欧盟,在控制抗生素使用和关注抗生素耐药性方面起步较晚[45]。2022 年 5 月国务院办公厅印发《新污染物治理行动方案》中指出,需规范抗生素使用管理,加强兽用抗菌药监督管理。虽然相对于地表水来说,地下水不易受到直接污染,但在地下水中仍发现了包括抗生素在内的多种污染物[46]。

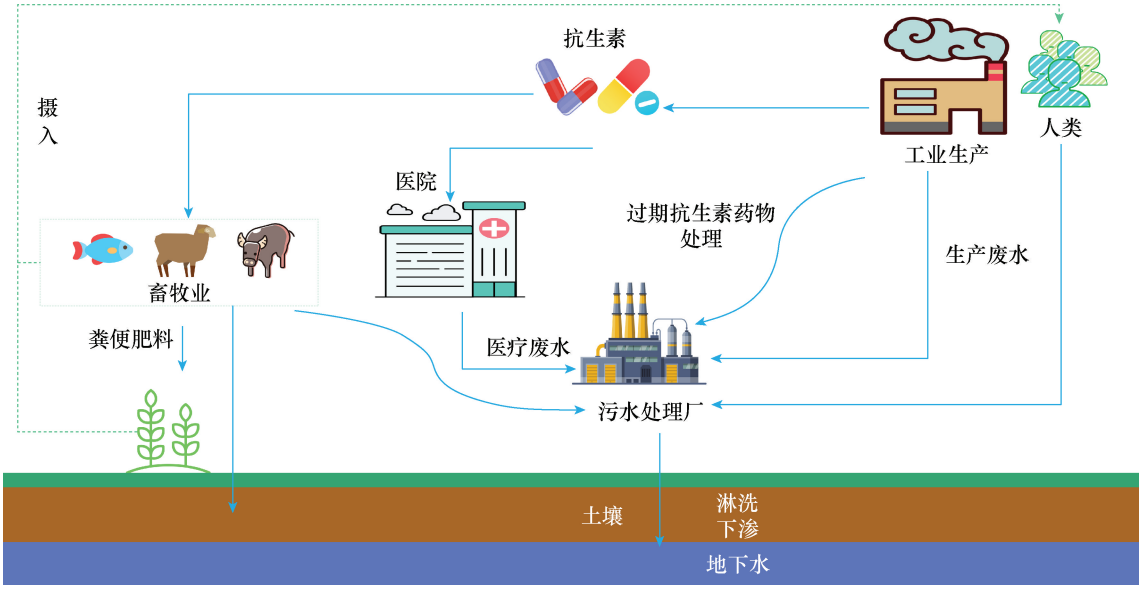


图 1　地下水中抗生素的污染来源和迁移途径

Fig. 1　The figure mainly describes the pollution sources and migration routes of antibiotics in groundwater. Antibiotics and their metabolites enter surface water or soil through direct or indirect means, and finally collect into groundwater through leaching or infiltration. The main sources of antibiotics in groundwater can be divided into production sources, use sources and discharge sources.

2.1　中国地下水中 28 种抗生素检出情况

为了更好地了解中国地下水中抗生素的污染现状,本文将黄福杨[47]所筛选的中国环境介质中检出次数超过 100 次的 28 种抗生素作为目标抗生素,收集了近十年中国地下水中抗生素检出浓度。检出浓度数值以平均值计,未给出平均值则按照最大值计。

由图 2 可知,地下水中常检出的 28 种抗生素的浓度变化超过 4 个数量级,从 0.1ng/L 到 1000ng/L 以上,检出频率较高的抗生素为:诺氟沙星、氧氟沙星、磺胺甲恶唑、恩诺沙星、磺胺嘧啶、红霉素等。

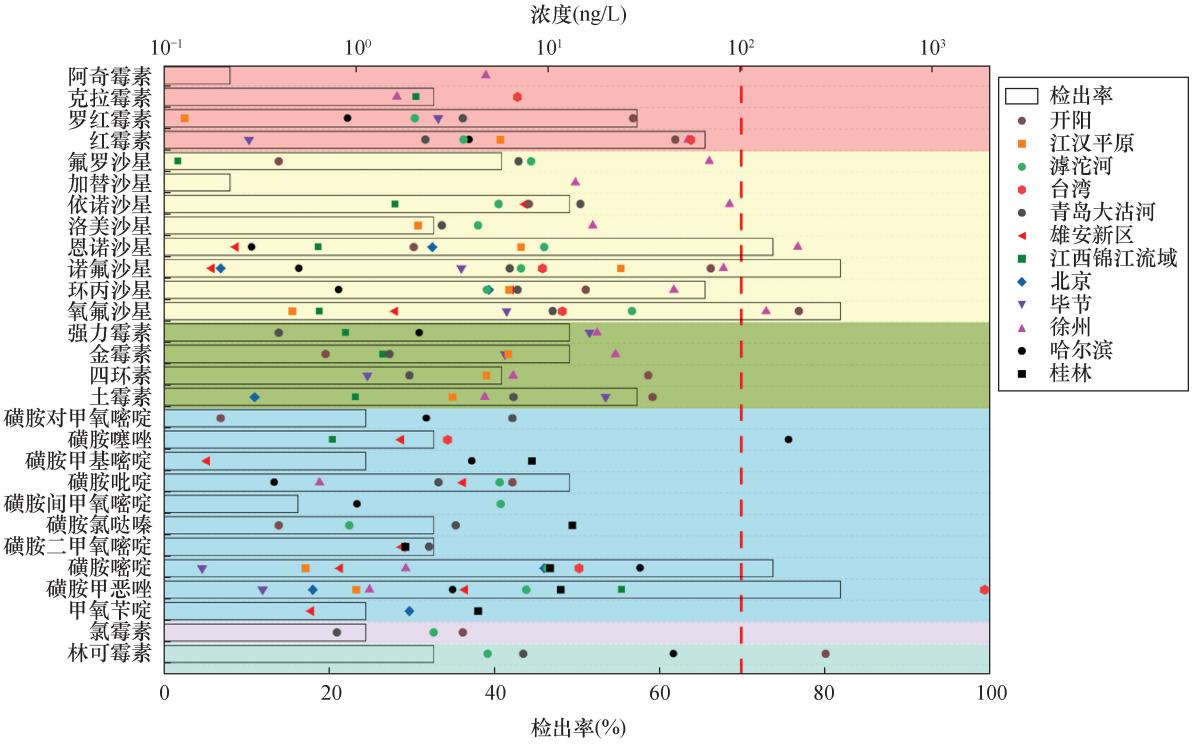
台湾地区磺胺甲恶唑的检出浓度高达 1820 ng/L,可能是由于磺胺类抗生素含有亲水性基团,更容易通过地表水迁移到地下水,而且磺胺甲恶唑也是台湾地区废水中最常检出的化合物之一,废水中残留的抗生素可能通过下渗转移到地下水中,与前文中所提到的地下水中抗生素的排放来源一致。江苏徐州地区相较于其他地区抗生素检出浓度高,主要是因为采样点在养殖场附近,抗生素通过动物粪便等排泄物进入环境,最终到达地下水。广东开阳和广西桂林为岩溶地下水,岩溶含水层结构的特殊性决定了污染物更容易进入地下水,因而开阳地区和桂林地区检出抗生素的浓度较高于其他地区。

由此可见,地下水中抗生素的浓度受抗生素性质、污染源位置、水文地质结构和使用量及排放量共同控制。

2.2　不同类抗生素在不同地区地下水中的检出情况

从图 3 可知,对地下水中抗生素的研究主要集中在华北、西南地区,在东北地区磺胺类抗生素检出最多,在华北、华东地区喹诺酮类抗生素检出最多,在西南地区喹诺酮类和四环素类抗生素检出最多,但对西北地区地下水中抗生素的研究程度比较低。

目前为止,受分析方法检出限及检出种类限制,



参考来源:北京[48]、雄安新区[49]、滹沱河[50]、哈尔滨[51]、江西锦江流域[52]、徐州[53]、江汉平原[54]、桂林[55]、毕节[56]、开阳[57]、台湾[58]、青岛大沽河[59]。

图 2　中国地下水中 28 种常见抗生素的检出情况

Fig. 2　Twenty-eight antibiotics with high detection frequency in environmental media in China were selected as target antibiotics, and the concentrations of antibiotics detected in groundwater in China in the past ten years were collected. The detected concentration value is calculated as the average value, or the maximum value is calculated if the average value is not given. It can be seen that the concentration of 28 antibiotics commonly detected in groundwater changes by more than 4 orders of magnitude, from 0.1 to more than 1000ng/L, and the antibiotics with high detection frequency are norfloxacin, ofloxacin, sulfamethoxazole, enrofloxacin, sulfadiazine, erythromycin other antibiotics.

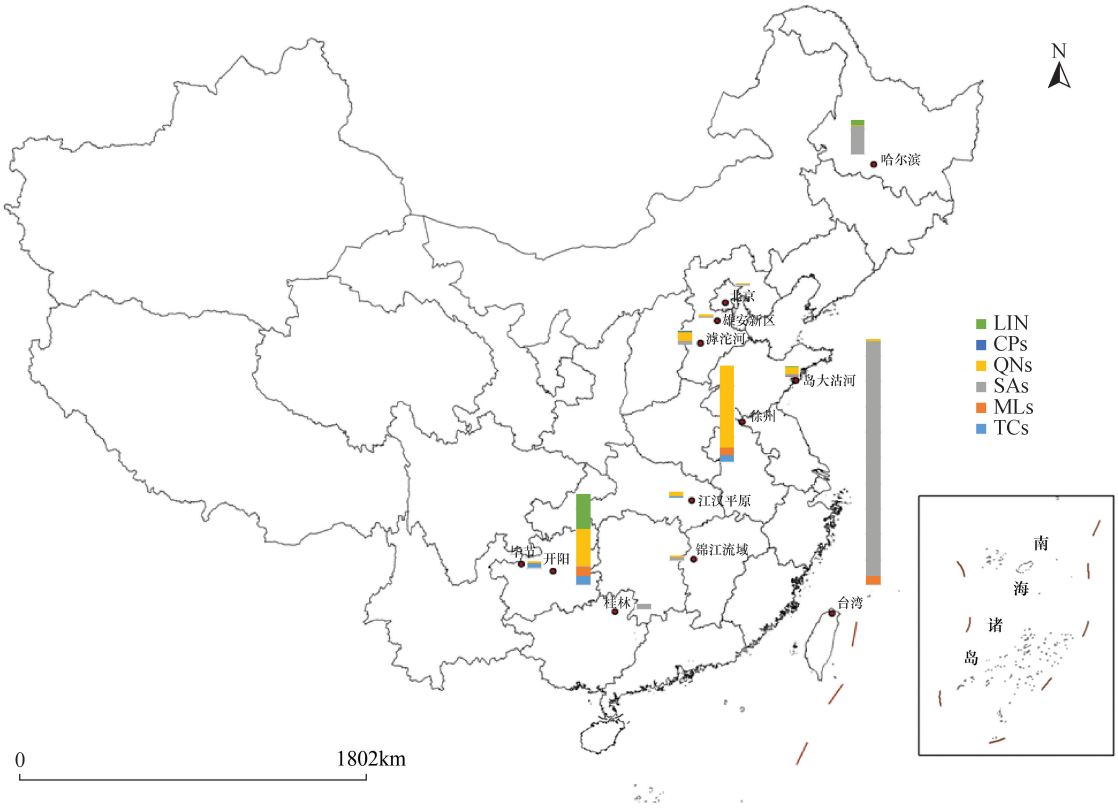


图 3　不同种类抗生素在中国不同地区地下水中的检出情况

Fig. 3　The antibiotics in the same place were added according to the categories, showing the detection of different classes of antibiotics in groundwater in different areas. It can be seen that the research on antibiotics in groundwater is mainly concentrated in North and southwest China. Sulfa antibiotics are the most detected in northeast China, quinolones are the most detected in North and East China, quinolones and tetracycline antibiotics are the most detected in southwest China, but the research level of antibiotics in groundwater in northwest China is relatively low.

我们仍不能对地下水中的抗生素作出全面的调查及评价。而抗生素的大量生产和使用使得其在地下水中累积并长期存在,且抗生素在地下水中的迁移转化复杂,形成了多种代谢产物,威胁生态环境及危害人体健康,对地下水中抗生素及其产物的定性定量分析变得越来越重要。

3　抗生素检测定性定量方法及进展

由于抗生素种类繁多,且在环境中浓度低,其结构不同导致其理化性质也各不相同,复杂的环境介质对其定性定量分析的准确性亦有影响,建立灵敏度高、特异性强的多组分同步分析的方法,一直是研究抗生素领域的一个关键课题[33]。

3.1　抗生素定性检测方法

针对抗生素定量检测方法多种多样,且技术不断地完善和发展,而对于环境中抗生素残留的定性研究报道则较少。目前抗生素的定性分析方法主要有微生物抑制法、薄层色谱法、气相色谱-质谱(GC-MS)联用技术、高效液相色谱-核磁共振联用技术和液相色谱-质谱(LC-MS)联用技术。前 4 种方法的原理、优缺点及适用范围列于表 1,液相色谱-质谱联用方法在下文中进行了详细介绍。微生物抑制法主要定性回答是否存在抗生素,薄层色谱法可以达到有效地分离而给出有多少种抗生素,要明确抗生素的种类还需要高效液相色谱-核磁共振联用和 LC-MS 联用技术。

LC-MS 联用技术是目前最常用抗生素分析方法,该方法灵敏度高、检出限低并且可以对多种抗生素进行同时测定分析。抗生素分子随着流动相在固定相上进行分配,固定相对于不同抗生素有不同的固定能力,所以不同抗生素在固定相中滞留时间不同,我们一般根据保留时间及出峰面积对抗生素进行定性定量分析[60]。LC-MS 与 GC-MS 联用技术不同,它采用电喷雾离子源(ESI)对化合物进行软电离,且不同型号的仪器其设计原理和参数不同,所以即使对同一化合物进行测定,也不能形成稳定、统一的碎片

表 1　抗生素定性方法

Table 1　Qualitative methods for antibiotics analysis

抗生素定性方法	方法原理	方法优缺点	方法适用范围
微生物抑制法（Microbial Inhibition Technique，MIT）	传统的测定方法，利用抗生素对微生物的生理机能、代谢的抑制作用，与阴性对照进行对比，判断是否存在抗生素[60]	操作简单，但灵敏度低，特异性差，且相似抗生素之间干扰性大[61]	动物性食品中抗生素残留[62]
薄层色谱法（Thin Layer Chromatography，TLC）	利用各成分对同一吸附剂吸附能力不同，从而达到各成分相互分离的目的	具有设备简单、操作简便等优点[63]，但样品处理复杂，且灵敏度低[64]	可用于快速分离和定性少量分析物质
气相色谱-质谱联用（Gas Cluomatography-Mass Spectrometry，GC-MS）	利用样品在色谱柱中气相和固定相间分配系数的不同，经过反复多次分配从而实现分离[65]	具有稳定性好、重复性强、操作简单和扩容性强及普适性大等优点，但不适用于极性大、难挥发的有机污染物[59]	应用于农药和易挥发性有机污染物的定性检测
高效液相色谱-核磁共振联用（HPLC-NMR）	利用 HPLC 分离复杂化合物，NMR 波谱确证未知化合物的结构[66]	该方法相较于质谱检测技术，灵敏度较低，且分析成本高	可用于分析化合物的组成、结构及其变化规律，被广泛应用于化学、医学等行业[67]

离子图，故 LC-MS 没有成熟的质谱图库[59]，不能同 GC-MS 一样在缺少标准物质的情况下获得定性结果，但可以通过质谱图中的分子离子峰、离子峰丰度比等参数以及待测化合物的保留时间来进行辅助定性分析。要获得确定的定性结果，还需要与标准物质在相同分析条件下对谱图进行比对。

近年来，虽然抗生素检测技术发展迅速，地下水中的抗生素已经可以使用 HPLC-MS/MS 等技术进行准确的定量分析，但是一次性可分析鉴定的数量仍然有限，检出抗生素的个数被检测方法包含的目标抗生素的个数所限制，难以满足实际需求。在 2005—2016 年期间，中国的 7 条主要河流和 4 个海域的水体和沉积物样本中共检测出 94 种抗生素[26]。黄福杨[47]筛选了近十年有关抗生素的文献，通过统计分析表明，在中国环境介质中共检出 105 种抗生素，但目前使用 HPLC-MS/MS 检测地下水中抗生素的方法最多包含 83 种抗生素[68]，不能全面包含使用频率和检出频率高的抗生素。为了对水环境中所存在的抗生素种类进行初步识别和全面了解，郎杭[59]在特定分析条件下建立了 UPLC-MS/MS 定性谱库，该谱库包括 189 种临床常见病药物的质谱信息，其中包含 84 种抗生素。该谱库后续可以通过增加抗生素的质谱信息，拓宽可定性的抗生素的种类。在特定分析条件下利用该谱库可对地下水中的抗生素进行半定性识别，基于半定性识别结果，选出检出频率高的抗生素进行确认和定量分析。

3.2　抗生素定量检测方法

目前常用的定量检测方法有酶联免疫法、毛细管电泳法、LC-MS 联用方法等。酶联免疫法不能同时检测多种组分；毛细管电泳法虽具有高效、快速、分离模式多的特点，但该方法灵敏度低且对抗生素分析的重现性较差；而 LC-MS 联用方法相较于以上两种方法具有灵敏度高、选择性好和定性定量准确的优点，是目前已知文献报道较多且较为成熟的检测水体中痕量抗生素的方法。

3.2.1　酶联免疫法

酶联免疫法（ELISA）是指在免疫基础上，将抗原与抗体特异性结合进行分析的一种方法[69]。它常被用于现场检测，但因其不能同时检测多种组分，主要用于环境中抗生素的初步筛查[70]。相较于其他检测方法，其灵敏度不高，而且还容易出现假阳性[71]。马建国[72]建立了磺胺类抗生素间接竞争 ELISA 免疫检测方法，检出限为 2.64μg/L。

3.2.2　毛细管电泳法

毛细管电泳法（CE）是以石英毛细管柱为分离通道、高压直流电场作为驱动力的一种新型液相分离技术[73]，依据待测样品中各组分之间淌度和分配行为上的差异来实现分离。该方法具有高效、快速、分离模式多的特点，但灵敏度低且对抗生素分析的重现性较差[74]，一般常与紫外检测器、质谱仪等联用来降低检测检出限。

3.2.3　液相色谱-质谱联用方法

目前常用的方法为 LC-MS 联用法。该方法适用于热不稳定、热挥发、强极性化合物的检测，通常使用该方法对抗生素进行定性定量分析[75]，广泛用于海水[76]、饮用水[77]、地下水[78]、沉积物[79]和食品[80]等不同介质中残留抗生素的检测。随着技术发展和检测需求的增加，陆续涌现出多种质谱检测

器。常见的质谱检测器有四极杆-线性离子阱质谱(Q-Trap)、三重四极杆质谱(QqQ)等,其中 QqQ 因具有较低的检出限,常用于多组分痕量分析[81]。

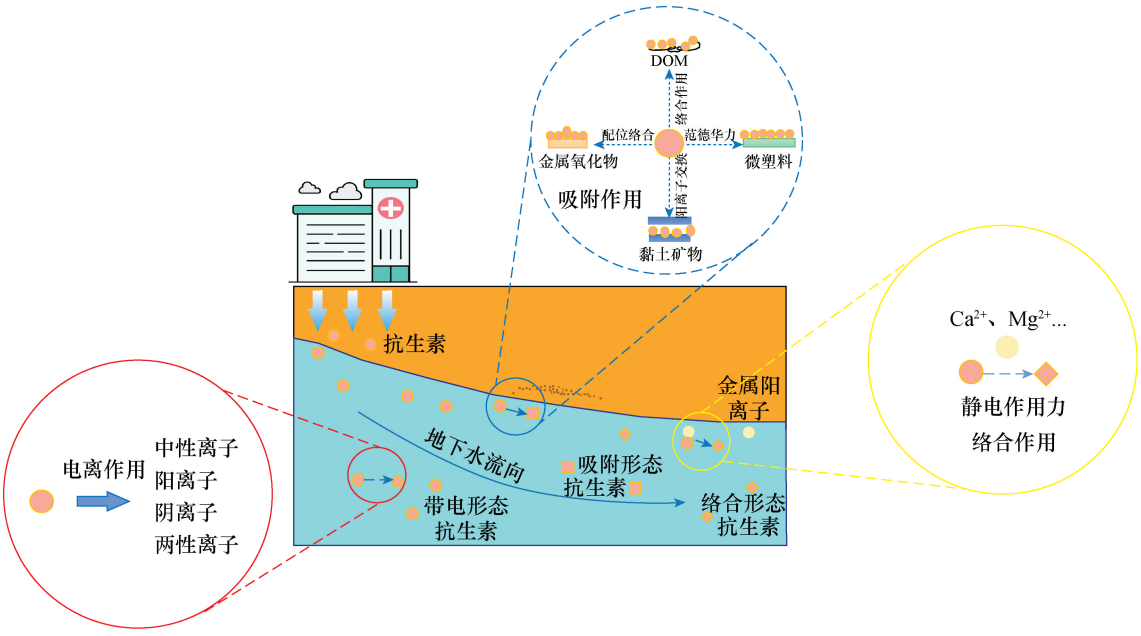
超高效液相色谱-串联三重四极杆质谱仪(UPLC-MS/MS)相较于传统液质联用方法增加了分析的通量、灵敏度及色谱峰容量,提高了分辨率和灵敏度[82],并显著减少了样品分析时间和流动相溶剂的消耗,因其灵敏度高、检出限低、多通量多组分同时检测污染物等优点,多应用于有机污染物定量检测[83]。宋焕杰等[84]应用固相萃取(SPE)和 UPLC-MS/MS 建立了 15 种抗生素检测方法;祁彦洁[85]建立了 35 种抗生素定量方法;Holton 等[86]建立了 54 种抗生素定量方法;郎杭[59]建立了 64 种抗生素定量方法,对地下水中抗生素进行检测,检出限为 0.41~14.71ng/L,90%的目标抗生素的基质加标回收率在 50%~120%范围内。

抗生素在环境中以痕量级存在,而环境样品复杂,所以分离和纯化基质中的抗生素的预处理过程往往成为分析测定的关键步骤[12]。因 SPE 的高回收率及高重现性,我们一般采取 SPE 对液体样品中的抗生素进行富集。由于大多数抗生素的极性较大,因而 HLB 小柱或膜片对不同的抗生素均有较好的富集效果。抗生素在不同 pH 下以不同的形态存在[87],HLB 小柱或膜片对不同形态的抗生素的富集效果也不同,上样前调节样品至合适的 pH 成为前处理的关键步骤。此外,因地下水中钙、镁等阳离子含量较高,在前处理过程中加入乙二胺四乙酸二钠(Na_2EDTA)用以络合,抑制阳离子与抗生素之间发生络合作用,可以提高目标抗生素的回收率[88]。

除了分析仪器本身会影响抗生素分析的检出限和回收率外,抗生素在水质样品中的存在形态也会对准确度和精密度产生影响。

4　抗生素的存在形态及环境行为

环境因素和理化性质会影响抗生素在地下水中的环境行为[89]。在地下水中,抗生素可能以带电形态、络合形态、吸附形态存在,具体表现形式及形成机理如图 4 所示。当抗生素与金属离子共存时,在一定条件下会发生络合反应,形成抗生素-金属复合物,影响抗生素吸附、氧化降解、光降解等行为;或



吸附态抗生素表现形式基于秦晓鹏等[90]修改。

图 4　抗生素在地下水中的三种存在形式及形成机理

Fig. 4　The figure mainly describes three existing forms and formation mechanisms of antibiotics in groundwater. In groundwater, antibiotics may exist in ionized form, complex state, adsorption state and so on. At different pH, antibiotics may exist in neutral, cationic, anionic or zwitterionic forms. When they coexist with metal ions, complexation reaction will occur under certain conditions to form antibiotic-metal complex. In addition, antibiotics may also exist in the adsorbed state, promoting or inhibiting antibiotic degradation. When antibiotics exist in charged form, complex form and adsorption form, they will also affect the accuracy of detection of antibiotic residue content in the environment.

以吸附态形式存在,促进或抑制抗生素降解。而当抗生素以带电形态、络合形态和吸附形态存在时,也会影响环境中抗生素残留含量检测的准确性。如仲小飞等[91]指出氧氟沙星会与地下水等水体中的阳离子或溶解性有机物发生络合作用,在测定时会使峰面积有一定程度的降低。陈小燕等[92]则指出四环素类抗生素与金属离子形成螯合物会吸附在反向色谱柱上,产生拖尾现象。

4.1　抗生素的带电形态

抗生素在不同 pH 条件下,可能以中性、阳离子、阴离子或两性离子形态存在[93],其环境行为也不同,并且影响其在地下水中含量检测的准确性,让预测抗生素的吸附和迁移变得更加复杂[74]。常见抗生素的酸解离常数及其在不同 pH 下的存在形式列于表 2。

以四环素(TC)为例,它有三个可电离的官能团,所以有三个酸解离常数[99]。如图 5 所示,在不同 pH 下,四环素分别以 H_3TC^+、H_2TC、HTC^-、TC^{2-} 的形式存在,各组分在水相中的分布取决于水相中 pH−p*K*a 的关系[100]。

基于抗生素的理化性质选择合适的前处理方法,是准确检测地下水中残留抗生素含量的关键步骤。前处理过程中,通常会调节样品 pH 后再经固相萃取仪萃取。因为不同目标抗生素在 HLB 小柱或膜片的保留能力与其本身的 p*K*a 值和 pH 有关,当抗生素以亲水的离子形式存在,不容易被用亲脂性吸收剂填充的 SPE 柱或膜片保留,其回收率会降低;当目标分析物以中性分子存在时,其回收率会增加[101]。祁彦洁[85]将水样调节至不同 pH,对比不同 pH 条件下各类抗生素的回收率,发现在 pH=2.5~3.0 和 4.5~5.0 时磺胺类抗生素回收率最高;喹诺酮类抗生素在 pH=2.5~3.0 时回收率最高;四环素类抗生素在 pH=4.5~5.0 时回收率较高;林可霉素以及大环内酯类抗生素在碱性条件下以分子态形式存在,利于富集。

表 2　常见抗生素的酸解离常数及存在形式

Table 2　Acid dissociation constants and existing forms of common antibiotics

抗生素类别	抗生素名称	p*K*a	pH 范围	抗生素形式	参考文献
四环素类	四环素(TC)	$pKa_1=3.3$ $pKa_2=7.7$ $pKa_3=9.7$	<3.30 3.30~7.70 >7.70	H_3TC^+ H_2TC HTC^-/TC^{2-}	[94]
磺胺类	磺胺噻唑(STZ)	$pKa_1=2.0$ $pKa_2=7.24$	<2.00 2.00~7.24 >7.24	STZ^+ STZ^0 STZ^-	[95]
大环内酯类	罗红霉素(ROX)	$pKa_1=9.08$ $pKa_2=12.45$	<9.08 9.08~12.45 >12.45	ROX^+ ROX^0 ROX^-	[96]
β-内酰胺类	头孢拉定(CED)	$pKa_1=2.63$ $pKa_2=7.27$	<2.63 2.63~7.27 >7.27	CED^+ CED^0 CED^-	[97]
喹诺酮类	环丙沙星(CIP)	$pKa_1=6.1$ $pKa_2=8.7$	<6.10 6.10~8.70 >8.70	CIP^+ CIP^0 CIP^-	[98]

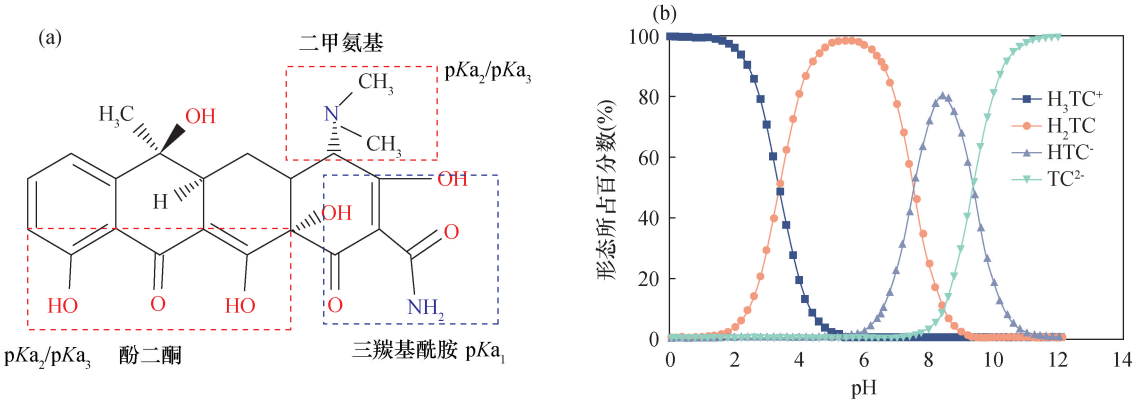


图 5　(a)四环素类抗生素结构式及(b)四环素在水中随 pH 变化的物质形态分布

Fig. 5　The figure shows (a) the structural formula of tetracycline antibiotics and (b) the material form distribution of tetracycline in water with pH change. It has three ionizable functional groups, so there are three acid dissociation constants. At different pH, tetracycline exists in the form of H_3TC^+, H_2TC, HTC^- and TC^{2-}, respectively. The distribution of each component in aqueous phase depends on the pH−p*K*a relationship in aqueous phase.

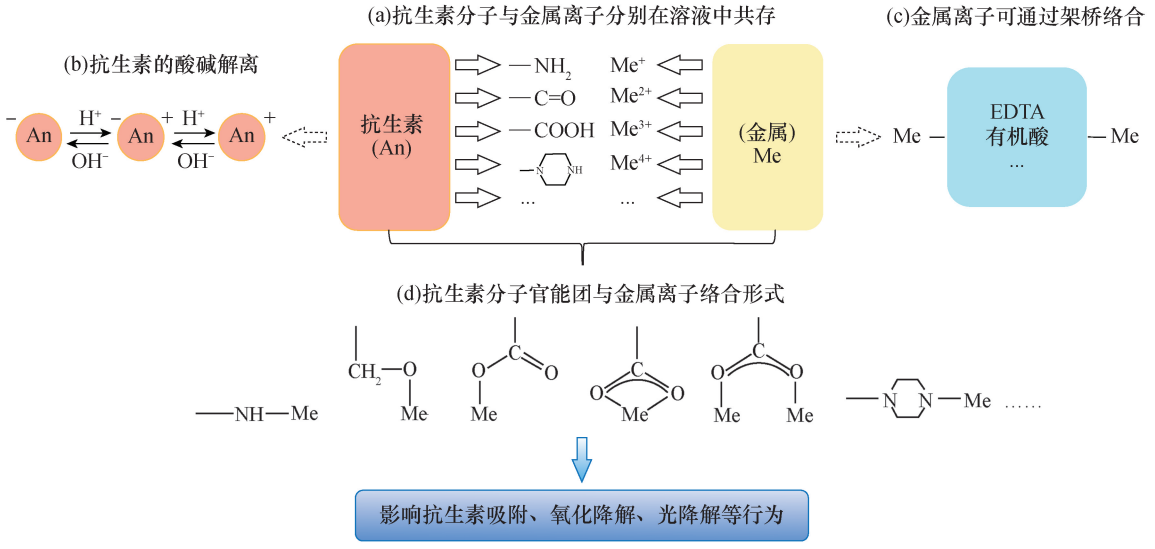
4.2　抗生素的络合形态

大多数抗生素含有能提供孤对电子的原子,易与金属离子发生络合作用[102],形成抗生素-金属离子络合物,并且含有 N、O 等富电子基团越多时,与金属离子的络合能力越强[103]。如喹诺酮类和四环素类抗生素都含有哌嗪基、羰基、羧基官能团,可以充当电子供体与金属配位,通过多种配位与金属结合,形成多种络合形态的混合物[104]。络合物的形成可能会使抗生素的环境行为(迁移、转化、毒性等)及生态效应发生改变。抗生素与水中金属的作用机理如图 6 所示。

抗生素与金属之间的络合作用会降低游离抗生素的含量,改变其形态分布,进而影响抗生素的活性,长期暴露在金属与抗生素的复合污染物中可能会导致多重抗性基因的产生与进化[105]。以四环素(TC)为例,TC 分子结构中存在羟基、羰基等易于解离的官能团,这些官能团会随着 pH 不同而发生质子化和去质子化,使得 TC 能有效地螯合各种金属阳离子[106],官能团受到 pH 等条件的影响,形成不同形式的四环素-金属离子复合物。因为金属离子特性和电子结构存在差异,不同的金属离子可以与 TC 发生的络合位置也会有所不同[107]。TC^-金属离子复合物的形成对 TC 在环境中的归趋有显著影响。钙镁离子与四环素类抗生素络合后会抑制细菌对于四环素类抗生素的摄取[100],相较于游离态的 TC,TC 与金属离子络合后在环境中更加稳定,影响水体中四环素的定量和定性分析结果[108]。祁彦洁[85]研究证明在地下水中四环素类抗生素易与 Ca^{2+}、Mg^{2+}等二价阳离子形成络合物,造成 TC 回收率只有 20%左右,但加入 Na_2EDTA 后明显提高了萃取回收率[59],此时 EDTA 通过竞争释放了结合态(或络合态)四环素类抗生素[109]。此外,当抗生素与金属离子发生络合反应,会影响抗生素的其他环境行为,例如黄翔峰等[103]指出金属离子络合会影响抗生素吸附、氧化降解、光降解等行为。

4.3　抗生素的吸附形态

抗生素在地下水中的迁移过程受其在含水介质上吸附的影响[89]。进入环境后,抗生素会通过解离、水解、光解和氧化还原等发生一系列的转化过程,抗生素的分子结构、憎水性、极性、可极化性以及空间构型都会影响抗生素在颗粒表面的吸附能力[96]。抗生素的吸附强烈依赖于它的解离行为,而解离行为又受到 pH 的影响[110],导致其在矿物上会有静电吸附、络合吸附等不同的吸附方式,从而影响抗生素的生物活性[111]。除此之外,抗生素还可以与介质中的有机质或者颗粒物表面吸附位点通过色



基于黄翔峰等[103]修改。

图 6　抗生素与水中金属共存的作用机理

Fig. 6　The figure shows the mechanism of the coexistence of antibiotics and metal ions in water. Because most antibiotics contain atoms that provide lone pairs of electrons, they are prone to complexation with metal ions. The complexation between antibiotics and metals will reduce the content of free antibiotics, change their morphological distribution, and ultimately affect the adsorption, oxidative degradation, photodegradation and other behaviors of antibiotics.

散力、范德华力、氢键或者诱导力等分子间作用力,或者通过所带官能团与有机质或者其他化学物质发生络合。而当抗生素吸附在含水介质上时,其在地下水中是不易被有效检测的。

不同类型的矿物与抗生素之间的吸附能力和机理都有所不同[112]。黏土矿物作为固相介质的重要组成部分,吸附抗生素的能力很强[98]。张洪丹[96]研究了黏土矿物对于罗红霉素的吸附能力,发现因其结构构成中存在较多的官能团,颗粒物上的大量吸附位点被抗生素所占据,蒙脱石对离子型抗生素,如四环素、土霉素、环丙沙星和恩诺沙星显示出高吸附能力,环丙沙星因其双电离的结构特性通过阳离子交换作用吸附在蒙脱石上[98],四环素主要通过阳离子交换和表面络合吸附在蒙脱石上[113]。一般认为,黏土矿物对于抗生素的吸附是发生在黏土矿物的层间[114]。韦世平[115]指出蒙脱石晶内空间的复杂环境会阻碍恩诺沙星对光的吸收,导致蒙脱石表面恩诺沙星的光降解效率更低,但由于光照下蒙脱石能够产生 · OH 和 · O^{2-}使蒙脱石表面恩诺沙星的降解速率加快。

金属氧化物是土壤中的次生矿物,而铁氧化物又是金属氧化物中含量最丰富、性质最活跃的部分。铁氧化物包括水铁矿、针铁矿、赤铁矿和磁铁矿等,铁氧化物在水中水解而在表面形成大量的表面羟基,与抗生素结构中的羟基、酮基等官能团发生配位络合作用而产生表面吸附[92]。一般认为,铁氧化物对于抗生素的吸附是发生在铁矿物的表面,静电作用和表面络合作用是抗生素在针铁矿上吸附的主导作用[116]。吸附态的抗生素对于细菌仍具有杀灭作用,王阳[23]通过研究不同吸附态的左氧氟沙星对大肠杆菌杀灭作用也发现了这一点。盛峰[117]则指出青霉素分子中的特征官能团与针铁矿表面及吸附态锌之间的配位络合作用能够催化青霉素类抗生素快速水解。

溶解性有机物(DOM)广泛存在于地下水系统中,含有多种官能团,与抗生素之间的相互作用可能会影响抗生素的环境行为[118]。DOM 作为抗生素的螯合剂和吸附剂可以影响抗生素的传输、毒性和环境归趋。如 DOM 与 TC 的络合作用大大降低了微生物对 TC 的生物利用度及其对水生生物的毒性[119]。阳离子交换作用、氢键作用及静电作用是 DOM 与喹诺酮类抗生素的主要结合方式[120]。蔡学巍[121]指出 DOM 对于磺胺嘧啶的光降解过程有明显的促进作用。杨波等[122]研究指出溶解态的腐植酸部分表面官能团在水环境中容易发生电离作用,带负电荷,所以更容易与电离后的抗生素发生相互作用。

近年来环境中微塑料的检出比较广泛,与之共存的抗生素也会被水环境中的微塑料吸附,从而影响两种污染物的生态毒性和环境归趋[118]。李硕[110]指出微塑料因其比表面积大、吸附性强,可以作为载体吸附土壤-地下水环境中的抗生素,并且作为载体可以促进抗生素的迁移。

分析不同吸附态的抗生素可以用于评价不同吸附形态对微生物杀灭效应的差异,尤其是评价 ARGs 产生的差异,细化抗生素给环境和人类所带来的潜在效应,有效地管控抗生素在环境介质中存在的风险。

5　结语与展望

地下水作为重要的饮用水源,其抗生素污染问题不容忽视。本文收集了近十年来(2012—2021)地下水中抗生素的文献,在此基础上分析了中国地下水检出情况,发现受分析方法检出限及检出种类的限制,仍不能对地下水中抗生素作出全面地调查及评价。对于环境中抗生素的调查与评价,可首先通过定性分析识别主要类型,针对主要类型开展定量分析或长期监测,为抗生素环境效应研究提供数据支撑。当抗生素以不同的带电形态、络合形态、吸附形态存在时,因其理化性质不同会影响测定的准确性、环境行为和毒理学效应,因而开展抗生素的形态分析至关重要。且基于抗生素的理化性质选择合适的前处理方法,也是准确检测地下水中残留抗生素含量的关键步骤。

目前为止,由于受分析方法检出限及检出种类的限制,中国仍未对于地下水中抗生素作出全面调查及评价,而只有明确抗生素污染在中国地下水中的浓度水平和空间分布状况,才有助于深入了解法律和监管框架的建立[123]。综上所述,优化定性定量检测方法、分析抗生素的不同形态、全面调查地下水中抗生素和科学评价抗生素形态与生态毒理学效应的关系,是今后地下水中抗生素研究的重点内容。

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A Review of Current Status and Analysis Methods of Antibiotic Contamination in Groundwater in China (2012—2021)

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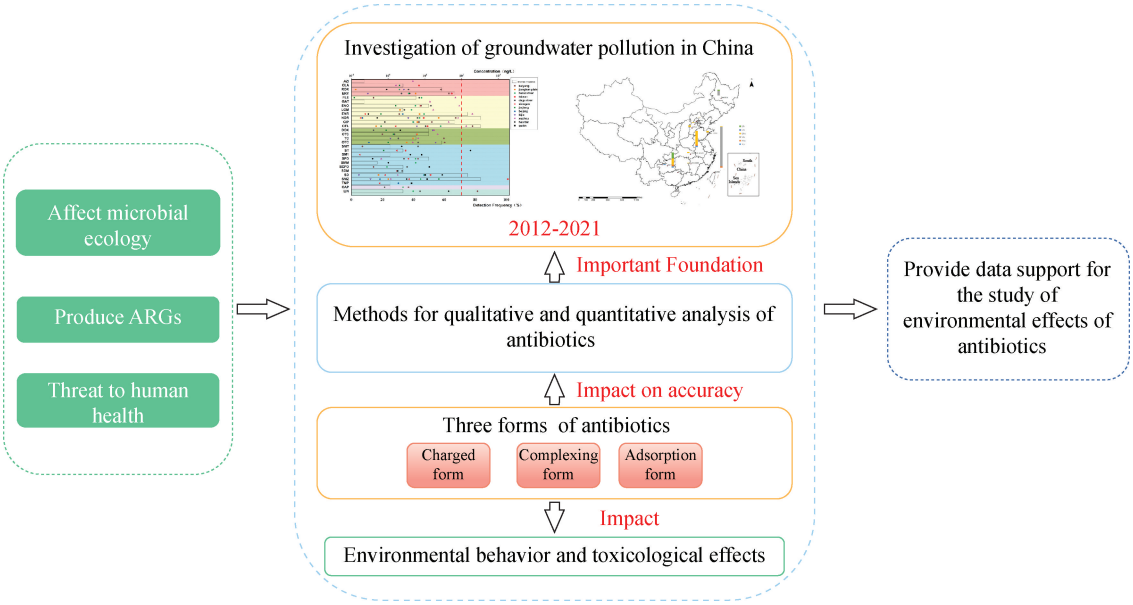
HIGHLIGHTS

(1) The concentrations of 28 antibiotics commonly detected in groundwater in China vary by more than 4 orders of magnitude.
(2) HPLC-MS/MS can perform accurate quantitative analysis of antibiotics in groundwater.
(3) The presence forms of antibiotics affect the recovery rate of pretreatment and the accuracy of qualitative and quantitative results.



ABSTRACT: As a form of new emerging pollutant, antibiotics have been detected in soil, surface water, groundwater, sediment and other different environmental media. As a major country in the production and usage of antibiotics, China's production and usage are increasing year by year. However, most antibiotics used for humans or animals cannot be fully absorbed and metabolized and will enter the environment in the form of prototypes or metabolites through waste and wastewater accumulating in soil and leaching into groundwater. Antibiotics entering the environment may affect microbial ecology, produce resistance genes, and even threaten human health. Compared with surface water, polluted groundwater is hidden, lagging and difficult to recover. The pollution of antibiotics in groundwater, as the main source of drinking water, has attracted much attention.

So far, the research on antibiotics in China is still mainly on surface water and soil, and there are few observations on antibiotics in groundwater. In order to systematically grasp the current pollution situation of antibiotics in groundwater in China, relevant literature on antibiotics in groundwater from 2012 to 2021 is reviewed in this paper. Twenty-eight antibiotics detected more than 100 times in environmental media in China were selected as target antibiotics, and the detected concentrations were summarized and analyzed. It was found that the concentrations of 28 antibiotics commonly detected in groundwater varied by more than 4 orders of magnitude, from 0. 1ng/L to more than 1000ng/L. The most frequently detected antibiotics were norfloxacin, ofloxacin, sulfamethoxazole, sulfadiazine, enrofloxacin, and erythromycin. Through comparative analysis of the detection of antibiotics in various places, it can be seen that the concentration of antibiotics in groundwater is controlled by the properties of antibiotics, the location of pollution sources, hydrogeological structure and the amount of usage and emissions. From the perspective of spatial distribution, sulfonamide antibiotics are the most detected in northeast China, quinolones are the most detected in North and East China, quinolones and tetracyclines are the most detected in southwest China, and the research on antibiotics in groundwater in northwest China is relatively low. So far, restrained by the detection limits and detection types of the analysis methods, a comprehensive investigation and evaluation of antibiotics in groundwater is not possible.

Due to the wide variety of antibiotics, their different structures lead to different physical andchemical properties. They exist in trace concentrations in the complex environment media, which also affects the accuracy of their qualitative and quantitative analysis. Therefore, the establishment of a sensitive and specific multi-component simultaneous analysis method has been a key issue for antibiotics research. The analysis methods of antibiotics are summarized, which are divided into qualitative analysis methods and quantitative analysis methods. The principle, advantages, disadvantages and application range of several antibiotic analytical methods are presented. These methods include microbial inhibition method (MIT), thin layer chromatography (TLC), gas chromatogram-mass spectrometry (GC-MS), high-performance liquid chromatogram-nuclear magnetic resonance (HPLC-NMR) and liquid chromatogram-mass spectrometry (LC-MS). Liquid chromatogram-mass spectrometry (LC-MS) is the most commonly used method for antibiotic analysis because of its high sensitivity, low detection limit and simultaneous determination of multiple antibiotics. With the rapid development of antibiotic analysis methods, some antibiotics in groundwater can be accurately quantified by using HPLC-MS/MS and other technologies. However, the number of antibiotics that can be analyzed and identified at one time is still limited. The research group of authors has established the qualitative spectrum library of common drugs by UPLC-MS/MS. In the future, the types of antibiotics that can be qualitatively identified in the spectrum library can be expanded by adding the mass spectrum information of antibiotics. Under specific conditions, the spectrum library can be used to carry out semi-qualitative identification of antibiotics in groundwater. At present, the commonly used quantitative detection methods include enzyme-linked immunoassay, capillary electrophoresis, and liquid chromatography-mass spectrometry. Compared with the other two methods, liquid chromatography-mass spectrometry has the advantages of high sensitivity, good selectivity and accurate quantitative ability. It is commonly used for the detection of trace antibiotics in reported water samples.

Antibiotics exist in the environment at trace levels and the matrix of environmental samples is complex, so the pretreatment process, including antibiotic separation, purification and concentration, often becomes the key step of determination. For example, the samples to be tested should be adjusted to an appropriate pH to enhance the enrichment of target antibiotics on HLB columns, and Na_2EDTA should be added to inhibit its complexation with calcium and magnesium and other metal ions in groundwater. The accuracy of antibiotic determination will be improved, and the detection limit will be lowered for water samples by solid phase extraction and the subsequent concentration process. In addition to the detection limit and recovery rate of antibiotics affected by the analytical instrument, the presence states of antibiotics in water samples will also affect the accuracy and precision.

Antibiotics may exist in the ionized state, complex state, adsorption state and other forms in groundwater. At different pH values, antibiotics may exist in neutral, cationic, anionic, orzwitterionic forms. When it coexists with metal ions, complexation reaction will occur under certain conditions to form antibiotic-metal complex which will reduce the peak area to a certain extent or cause tailing phenomenon on the reverse analytical column. The formation of the complex may also change the environmental behavior (migration, transformation, toxicity, etc.) and ecological effects of antibiotics. In addition, the analysis of antibiotics in different adsorption states can be used to evaluate the differences in microbial killing effects of different adsorption forms, especially the differences in ARG production and spreading. This will be helpful for accurately evaluating the potential effects on the environment or human beings and effectively controlling the risks of antibiotics in environmental media. Therefore, the existing form analysis of antibiotics is of great significance for the further accurate determination of antibiotics and the evaluation of environmental effects.

Up to now, limited by the detection limits and detected types of antibiotics in analytical methods, there has not been a comprehensive national-scale investigation and evaluation of antibiotics in groundwater in China. Only by clarifying the concentration level and spatial distribution of antibiotic pollution in China's groundwater can it help to understand the contents of relevant laws and regulations on new emerging pollutants and support the establishment of a regulatory framework for natural resources and the environment. In conclusion, optimizing qualitative and quantitative detection methods, analyzing different existing forms of antibiotics, comprehensively investigating antibiotics in groundwater, and scientifically evaluating the relationship between antibiotic forms and ecotoxicological effects are the main contents of antibiotics research in groundwater in the future.

KEY WORDS: groundwater; antibiotics; pollution status; environmental behavior; speciation analysis; HPLC-MS/MS