

**土壤中有机肥源抗生素抗性基因环境归趋与风险管理研究进展**

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## 土壤中有机肥源抗生素抗性基因环境归趋与风险管理研究进展

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**摘要:** 抗生素抗性基因——一类新型污染物, 已对人类健康和环境安全构成威胁, 如何有效应对日益严峻的耐药性危机已成为一项全球性挑战。有机肥源抗生素抗性基因是土壤抗生素抗性基因的主要来源, 而土壤参与并主导不同环境单元中抗生素抗性基因演化的多元交互作用, 因此, 有必要厘清有机肥源抗生素抗性基因在土壤和其他环境介质中的命运、归趋与风险。本文综述了近年来有机肥源抗生素抗性基因在土壤中的分布特征、环境归趋、人体暴露风险以及风险管理方面的研究进展, 并提出建议与展望, 以期为有效减轻抗生素抗性基因在环境中的危害, 遏制抗生素抗性基因的增殖与传播提供理论依据与决策参考。

**关键词:** 土壤; 有机肥; 抗生素抗性基因; 环境归趋; 阻控技术; 风险评估

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### Environmental fate and risk management of manure-borne antibiotic resistance genes in soil: A review

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**Abstract:** Antibiotic resistance genes (ARGs), as emerging contaminants, are posing a serious threat to human health and environmental security. How to effectively combat the increasingly severe resistance crisis has become a global challenge. ARGs derived from manure are the main source of ARGs in soil, and involved in the multiple interactions of antibiotic resistance evolution in different environmental

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components. Therefore, it is of great significance to clarify the fate, dynamics and risk of manure-borne ARGs between soil and other related environmental media. This prospectus reviewed the recent progresses in the distribution characteristics, environmental fate, human exposure risk and effective alleviation strategies of manure-borne ARGs around soil ecosystems, and advanced the recommendations for future research. This review can provide theoretical basis and decision-making reference for effectively reducing the risks of ARGs in the environment.

**Keywords:** soil; manure; antibiotic resistance gene; environmental fate; mitigation technology; risk assessment

作为20世纪医学史上的重要成就之一,抗生素自发现以来便广泛应用于畜牧业、农业、水产养殖业和医疗卫生等领域,为人类和畜禽疾病的治疗和动、植物生长的促进发挥着重要作用<sup>[1-2]</sup>。然而长期和大量使用抗生素会加速抗生素抗性基因(Antibiotic resistance genes, ARGs)的产生与传播,诱导抗生素抗性细菌(Antibiotic-resistant bacteria, ARB)的出现<sup>[3-4]</sup>。有报道指出,2019年全球有127万人直接死于抗生素耐药性,495万人的死亡与抗生素耐药性感染有关,远超过因疟疾和艾滋病死亡的人数<sup>[5]</sup>。预计到2050年,因抗生素耐药性造成的年均死亡人数将攀升至1 000万<sup>[6]</sup>。以ARGs和ARB为代表的抗生素耐药性正成为全人类共同面临的健康危机。早期的研究侧重于临床获得的抗生素耐药性,但忽略了抗生素耐药性在环境细菌种群中广泛存在,近些年有学者提出“one-health”理念,即抗生素耐药性可以通过多种生态系统进行传播,包括人类、动物、植物、水、空气和土壤的微生物组<sup>[7]</sup>。土壤作为ARGs最重要的载体,不仅本身含有大量ARGs,而且还接收来自地表水、地下水、大气及动植物来源的ARGs,是控制ARGs迁移与传播的核心<sup>[8]</sup>。因此,土壤生态系统中ARGs的污染与防控成为近年来国际研究的前沿与热点。

ARGs通过有机肥的施用、污泥农用、畜禽废水及污水灌溉、降水径流等方式进入土壤,其中动物粪便排泄与有机肥施用是ARGs进入土壤环境的主要途径<sup>[8-10]</sup>。在可移动遗传元件(Mobile genetic elements, MGEs)的介导下,有机肥源ARGs通过水平基因转移作用(Horizontal gene transfer, HGT)在土壤和其他环境介质中传播,而且能够通过食物链与环境暴露迁移进入人体微生物组和病原体中,最终导致人体产生抗生素耐药性<sup>[10-11]</sup>。本文将从土壤中有机肥源ARGs的产生、分布,有机肥源ARGs在土壤-土壤动物、土壤-植物、土壤-水和土壤-空气体系的环境归趋,有机肥源ARGs暴露引起的环境风险和风险管理技术三方面系统阐述相关研究进展,并提出建议与展望。

## 1 土壤中有机肥源ARGs产生与分布

### 1.1 有机肥中的ARGs

中国是畜禽养殖业大国,据统计,截至2020年底,我国大牲畜饲养数量为10 265万头,大规模的牲畜和家禽饲养会产生大量粪污,其中2015年我国规模化畜禽养殖产生粪污 $3.83\times10^9\text{ t}$ <sup>[12-13]</sup>。由于畜禽粪便具有提高土壤肥力、作物产量以及增加土壤微生物多样性的能力,因此畜禽粪便常直接或经过堆肥处理后施入农田土壤中<sup>[14-15]</sup>。然而,国内外的众多研究均在有机肥样品中检出了丰富的ARGs,这表明有机肥具有抗生素耐药性传播风险<sup>[16-20]</sup>。

多项研究表明,作为饲料添加剂使用的抗生素和重金属是导致有机肥中ARGs富集的重要驱动因子<sup>[17,19]</sup>。2019年中国兽药抗生素使用总量为30 903.66 t,每吨动物产品兽药使用量约为160 g<sup>[21]</sup>。进入动物体内的抗生素只有一部分能够被吸收利用,大部分以母体化合物和代谢物的形式随粪便与尿液排出体外<sup>[22-23]</sup>。长时间的抗生素积累会对环境细菌产生选择压力,加速ARGs和ARB的出现与传播。在服用抗生素的过程中,被动物肠道吸收的抗生素也会直接诱发肠道微生物产生抗生素抗性,研究人员在猪<sup>[24]</sup>、牛<sup>[24]</sup>、鸡<sup>[25]</sup>的肠道微生物中检测出了多种ARGs。一些维持生理功能所必需的微量元素(铁、钴、锌、铜、锰、钼、硒等),通常作为营养物质添加到动物饲料中<sup>[26]</sup>。有调查指出,猪饲料中重金属铜和锌的含量分别为标准的1.65~2.35倍和3.29~13.62倍<sup>[27]</sup>。动物对微量元素的吸收效率有限,猪粪便相比于饲料中铜、锌、砷、镉、铅和铬富集因子的平均值分别为4.68~6.11、3.43~4.60、2.30~3.12、2.89~4.63、2.45~5.00和3.32~5.00<sup>[27]</sup>。重金属的选择压力促进细菌重金属抗性基因(Heavy metal resistance genes, MRGs)的出现,MRGs能够与ARGs通过协同抗性、交叉抗性、协同调控和生物膜诱导作用进行交互传播,加速ARB的出现和扩散<sup>[28]</sup>。

### 1.2 土壤固有的ARGs

土壤是一种优质的天然微生物介质,具有微生物

生长繁殖所需的养分、水分、空气和温度。在长久的进化历程中,土壤微生物能够通过自发基因突变和相互作用产生 ARGs,其出现甚至早于人类开始使用抗生素<sup>[29~30]</sup>。即使在鲜有人为活动干扰的环境中,土壤微生物自身也存在抗生素耐药性,例如研究人员在南极研究站附近土壤中检测出了73种ARGs和MGEs,涵盖8种主要的抗生素耐药性类型<sup>[31]</sup>;同样地,VAN GOETHEM等<sup>[32]</sup>在南极不被干扰的原始土壤中鉴定出177个天然存在的ARGs,其中大多数编码一种或多种药物外排泵。QIAN等<sup>[33]</sup>在3种原生生态系统(阿拉斯加苔原、美国中西部大草原和亚马逊雨林)土壤中均观察到了较高多样性和丰度的ARGs。

### 1.3 土壤有机肥源 ARGs

尽管土壤微生物拥有本底ARGs,然而随着人类生产活动对土壤的影响,外源输入加速了土壤中抗生素耐药性的发生,其中主要的方式是畜禽养殖业产生的动物粪便经过堆肥后以有机肥的形式施用于农田土壤<sup>[10,34]</sup>。在国内外的施用有机肥土壤和畜禽养殖场土壤中普遍检出了多种ARGs和MGEs(表1)。外源有

机肥能够通过3种途径影响土壤中ARGs的丰度:(1)有机肥中的营养物质促进土壤原有的ARB生长与增殖;(2)有机肥中的ARB迁移并定植在土壤中,以及ARGs通过HGT作用转移至土壤微生物中;(3)有机肥中的抗生素和重金属等残留作为选择压力,导致土壤细菌后天获得抗生素耐药性,产生新的ARB<sup>[47]</sup>。

土壤中有机肥源ARGs的分布受土壤理化性质、土地管理方式、土壤污染特征和气候因子的影响。不同类型土壤的理化性质存在显著差异,从而会对ARGs的组成产生影响。例如,在长期施加有机肥的褐土、潮土和盐碱土中分别检出了141、175种和161种ARGs,其中MGEs介导的HGT是不同类型土壤ARGs分布的主要影响因子<sup>[48]</sup>。此外,土壤团聚体尺寸通过对MGEs水平、土壤特性和细菌丰度产生作用,间接影响施肥土壤中ARGs的分布特征,其中尺寸小于53 μm的土壤团聚体具有更高丰度和多样性的ARGs<sup>[49]</sup>。土地管理方式能够影响有机肥源ARGs分布特征,包括施肥历史、有机肥类型和耕作方式等因素。WANG等<sup>[50]</sup>研究发现旱地土壤与水稻土壤中

表1 不同土壤样品中检出的有机肥源ARGs

Table 1 Manure borne-ARGs detected in different soil samples

| 国家<br>Country | 地区<br>Region | 土壤和有机肥处理<br>Soil and manure treatment | 抗生素耐药性<br>Antibiotic resistance  | ARGs/MGEs绝对丰度<br>Absolute abundance of ARGs/<br>MGEs/(copies·g <sup>-1</sup> )  | 检测方法<br>Method of detection | 参考文献<br>Reference |
|---------------|--------------|---------------------------------------|--|---|-----------------------------|-------------------|
| 中国            | 广西           | 农田土壤和养猪场土壤                            | 17种ARGs, <i>IntII</i>  | —   | 实时荧光定量PCR(qPCR)             | [35]              |
|               | 四川           | 长期施用农家有机肥稻田土壤                         | 166种ARGs,9种MGEs  | 9.55×10 <sup>8</sup> ~2.83×10 <sup>10</sup> /<br>1.14×10 <sup>9</sup> ~2.29×10 <sup>10</sup>  | 高通量实时荧光定量PCR<br>(HT-qPCR)   | [36]              |
|               | 宁夏           | 养牛场周边土壤和施用牛粪土壤                        | 35~79种ARGs   | —   | 高通量实时荧光定量PCR<br>(HT-qPCR)   | [37]              |
|               | 云南           | 施用粪肥水稻土壤                              | 100种ARGs,9种MGEs  | 1.0×10 <sup>7</sup> ~1.3×10 <sup>10</sup>   | 高通量实时荧光定量PCR<br>(HT-qPCR)   | [38]              |
|               | 河北           | 养殖场猪粪和鸡粪堆放土壤                          | <i>tetW</i> 、 <i>tetC</i> 、 <i>tetG</i> 、 <i>tetL</i> 、 <i>sullI</i> 、<br><i>sullII</i> 、 <i>intII</i> | —   | 实时荧光定量PCR(qPCR)             | [39]              |
|               | 北京           | 施用鸡粪农田土壤                              | 61~73种ARGs   | —   | 高通量实时荧光定量PCR<br>(HT-qPCR)   | [40]              |
|               | 广东           | 施用鸡粪和猪粪菜地土壤                           | 13种ARGs,2种MGEs   | —   | 实时荧光定量PCR(qPCR)             | [41]              |
|               | 江苏           | 施用堆肥猪粪、堆肥鸡粪和堆肥牛粪农田土壤                  | 140种ARGs   | —   | 高通量实时荧光定量PCR<br>(HT-qPCR)   | [42]              |
|               | 山东/<br>天津    | 长期施用猪粪、鸡粪和牛粪菜地土壤                      | 50~84种ARGs   | 4.10×10 <sup>8</sup> ~1.97×10 <sup>10</sup> /<br>2.73×10 <sup>7</sup> ~3.57×10 <sup>9</sup>   | 高通量实时荧光定量PCR<br>(HT-qPCR)   | [43]              |
|               | 安徽           | 长期施用新鲜牛粪和猪粪农田土壤                       | 23~32种ARGs,3种MGEs  | 1.15×10 <sup>6</sup> ~7.21×10 <sup>11</sup> /<br>9.02×10 <sup>6</sup> ~1.15×10 <sup>11</sup>  | 实时荧光定量PCR(qPCR)             | [44]              |
| 澳大利亚          | 墨尔本          | 施用堆肥牛粪和堆肥家禽粪便菜地土壤                     | 67~82种ARGs,10种MGEs   | 4.37×10 <sup>9</sup> ~2.02×10 <sup>10</sup> /<br>1.23×10 <sup>9</sup> ~6.94×10 <sup>9</sup>   | 高通量实时荧光定量PCR<br>(HT-qPCR)   | [45]              |
| 美国            | 弗吉尼亚州        | 长期施用添加抗生素的牛粪草场                        | 33种ARGs  | <i>blaSHV</i> : 7.94×10 <sup>5</sup> ~2.00×10 <sup>9</sup><br><i>intII</i> : 1.00×10 <sup>5</sup> ~2.51×10 <sup>7</sup><br><i>floR</i> : 1.00×10 <sup>2</sup> ~6.31×10 <sup>6</sup><br><i>mexB</i> : 1.00×10 <sup>1</sup> ~3.98×10 <sup>7</sup> | 微流控定量PCR(mfqPCR)            | [46]              |

ARGs 的差异强于历史施肥模式(化肥和粪便堆肥),水稻土具有更高的微生物量与 ARGs 累积水平。YUAN 等<sup>[51]</sup>研究发现施加粪肥土壤中 ARGs 的变化模式主要取决于肥料类型,其中猪粪的影响大于牛粪与家禽粪便。此外,土壤中残留的污染物胁迫会通过促进水平基因转移的发生,增加土壤的抗生素耐药性<sup>[52]</sup>,例如非抗生素药物<sup>[53]</sup>、消毒剂<sup>[54]</sup>、农药<sup>[55-56]</sup>、多环芳烃<sup>[57-58]</sup>、石油烃<sup>[59]</sup>、微塑料<sup>[60]</sup>和重金属<sup>[58]</sup>等。值得注意的是,气候因子作为影响土壤抗生素耐药性的重要因素常被忽略,近期的一项模拟气候变暖的研究发现,增温对 ARGs 数量和丰度的积极影响取决于采样季节,季节性是影响森林土壤 ARGs 组成模式的关键因素<sup>[61]</sup>。

## 2 土壤中有机肥源 ARGs 的环境行为

### 2.1 ARGs 在环境中的转移机制

施用有机肥的土壤是发生 HGT 的热点区域,有机肥中携带的众多 ARGs 和 ARB 能够在土壤中转移和繁殖<sup>[60,62]</sup>。不同宿主菌之间 ARGs 的水平转移包括 3 种类型:接合(Conjugation)、转化(Transformation)和转导(Transduction)。接合需要细胞间通过性菌毛进行接触使 ARGs 从供体细胞进入受体细胞中,这是 HGT 最主要的途径<sup>[52,63]</sup>。转化是指环境中的游离

DNA 被细胞吸收并获得相应的遗传性状,转化发生前提条件是受体细菌必须具有转化能力,外源 DNA 通过细胞染色体 DNA 吸附整合或直接转移至质粒 DNA,最终进入受体基因组<sup>[64-65]</sup>。转导需要噬菌体的参与,噬菌体充当载体与不同细菌作用,从而将 ARGs 转移至受体菌中<sup>[66]</sup>。

尽管目前的研究更多着眼于 HGT,但是随着研究技术的发展,越来越丰富的研究证实有亲缘关系的细菌中通过繁殖作用发生的垂直基因转移(Vertical gene transfer, VGT),在 ARGs 的传播中起着同样重要的作用。LI 等<sup>[67]</sup>通过单细胞微流体与时间延迟成像技术分辨了以大肠杆菌为受体时,ARGs 转移过程中 VGT 和 HGT 的贡献,实验初期的转移以 HGT 作用为主,在实验开始 4 h 后通过 HGT 作用形成的转化结合子趋于饱和;随后 VGT 作用逐渐加强,在 6 h 时通过 HGT 和 VGT 形成的转化结合子的总数分别为 3.0% 和 4.3%。WEI 等<sup>[68]</sup>采用高通量单细胞技术与 epicPCR 技术同时对 *sull* 和 16S rRNA 进行探究,特异性地跟踪 ARGs 宿主细菌的动态,发现在 ARGs 转移中 HGT 发挥 54% 的作用,VGT 发挥 46% 的作用。

### 2.2 土壤中有机肥源 ARGs 的归趋特征

有机肥源 ARGs 进入土壤后,在 HGT 和 VGT 作用下通过多种环境介质进行迁移与传播(图 1),包括土

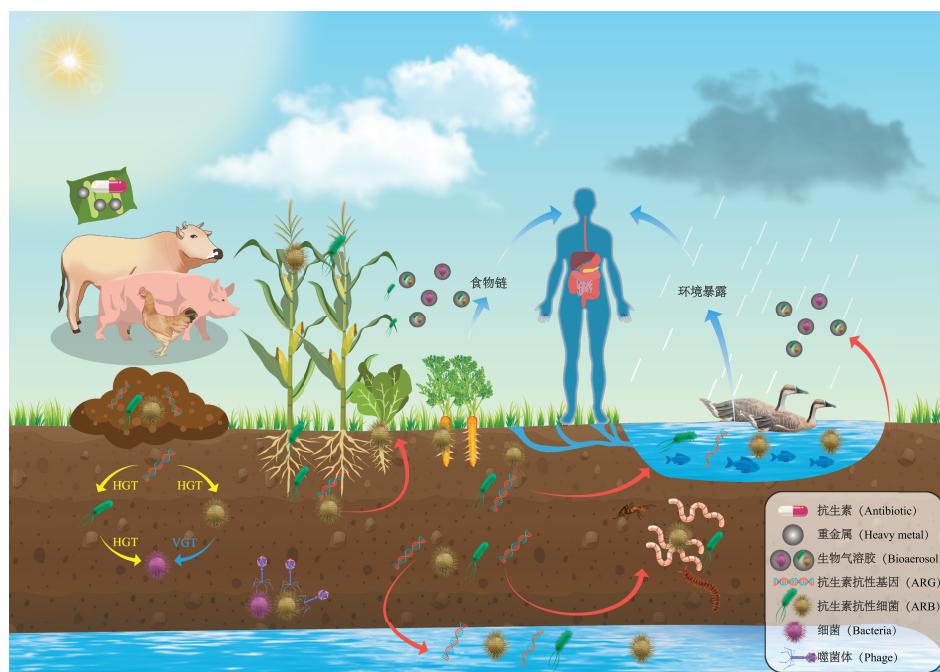


图 1 有机肥源 ARGs 在土壤生态系统中的传播

Figure 1 Transmission of manure-borne ARGs in the soil ecosystem

壤、土壤动物、植物、水和大气,最终经过食物链和环境暴露影响人体健康。

### 2.2.1 土壤吸附游离 ARGs

由于土壤具有团聚体结构、高有机质含量和丰富的表面官能团,携带 ARGs 片段的游离 DNA 进入环境中后能够被土壤颗粒吸附,从而保护其不被环境中的酶降解<sup>[69]</sup>。关于胞外 DNA 在土壤中的持久性已有一些研究,WANG 等<sup>[70]</sup>采用改良的外源质粒模拟胞外 DNA,探究了土壤中胞外 DNA 的动态变化,结果表明胞外 DNA 在土壤中可以存在超过 4 周;SIROIS 等<sup>[71]</sup>研究发现土壤中胞外 DNA 的降解速率与土壤湿度和温度呈正相关关系,与土壤有机碳含量呈负相关关系。

### 2.2.2 ARGs 在土壤-土壤动物中的迁移

蚯蚓、线虫、跳虫等土壤动物是土壤生态系统的重要组成部分,也是土壤 ARGs 迁移的重要载体,而有机肥施用可能会促进土壤动物对 ARGs 的富集。研究发现土壤动物样品中可检出的 ARGs 达到 265 种,其中耕地土壤动物 ARGs 相对丰度和数量分别高出森林土壤动物 16.4% 和 15.8%<sup>[72]</sup>。土壤动物捕食链是 ARGs 转移的潜在途径,一项研究检测了长期施用有机肥的土壤中线虫和蚯蚓肠道的微生物抗性,结果显示在土壤、线虫和蚯蚓肠道之间共享 38 个 ARGs,且线虫肠道对 ARGs 的富集水平高于蚯蚓,表明土壤-线虫-蚯蚓的食物链是土壤生态系统中 ARGs 转移的潜在途径<sup>[73]</sup>。影响土壤动物肠道微生物中 ARGs 组成的因素是多样的,DING 等<sup>[74]</sup>通过部分冗余分析发现,蚯蚓肠道微生物组成对 ARGs 变化起主导作

用,长期施用有机肥会改变土壤动物肠道微生物的结构与组成,其次为土壤环境因子和 MGEs。CHAO 等<sup>[75]</sup>采用可培养细菌分离与高通量测序结合的手段,从蚯蚓肠道中分离出 87 株具有四环素类和/或磺胺类抗性的可培养菌株,并发现蚯蚓肠道细菌群落中普遍存在四环素类和磺胺类抗性基因,表明蚯蚓肠道是耐药菌定殖的热点区域。

### 2.2.3 ARGs 在土壤-植物中的迁移

植物,特别是可食用农作物,能够作为 ARGs 传播的潜在载体<sup>[76]</sup>。有机肥源 ARGs 能够在植物中迁移与富集,国内外的研究均在施加有机肥土壤种植的农作物中检出了丰富的 ARGs(表 2)。不同植物器官与组织对 ARGs 的富集程度具有差异性。植物根际是微生物活动和 HGT 的热点区域,以施用粪肥的玉米为研究对象,根际土壤中 *ermC* 和 *ermX* 在 63 d 中的相对丰度增幅分别为 103.0% 和 71.5%,表明玉米根际有利于大环内酯类抗性基因的富集<sup>[81]</sup>。ZHANG 等<sup>[45]</sup>在生菜根际土壤、根系内生组织和叶系内生组织中检测出了 25 个共享 ARGs,表明这些基因可能从土壤转移至生菜内部组织。施加有机肥会增加叶面 ARGs 的丰度与多样性,这是因为叶面具有巨大的表面积,能够通过植物根际与内生组织从土壤中获得 ARGs,或者直接从空气中获得 ARGs<sup>[77,82]</sup>。植物内生组织的 ARGs 水平常低于叶面和根际,然而内生组织中的 ARGs 不能通过洗涤与消毒除去,摄入后有将 ARGs 传播至人体内的潜在风险<sup>[40,45,83]</sup>。

土壤中有机肥源 ARGs 向植物迁移的过程是多

表 2 不同植物样品中检出的有机肥源 ARGs

Table 2 Manure borne-ARGs detected in different plant samples

| 国家<br>Country | 地区<br>Region | 植物和有机肥处理<br>Plant and manure treatment | 抗生素耐药性<br>Antibiotic resistance   | ARGs/MGEs 绝对丰度<br>Absolute abundance of<br>ARGs/MGEs/(copies·g <sup>-1</sup> )             | 检测方法<br>Method of detection | 参考文献<br>Reference |
|---------------|--------------|--|---|--|-----------------------------|-------------------|
| 中国            | 广西           | 施用猪粪的豌豆、生菜、白菜、芹菜、空心菜、葱和香菜              | 根:16 种 ARGs, <i>IntI</i> ;叶:14 种 ARGs, <i>IntI</i>                            | —  | 实时荧光定量 PCR(qPCR)            | [50]              |
|               | 北京           | 施用猪粪的香菜、莴苣、生菜和白菜                       | 根:16~57 种 ARGs;叶:11~18 种 ARGs   | —  | 高通量实时荧光定量 PCR<br>(HT-qPCR)  | [55]              |
|               | 山东           | 施用鸡粪的玉米                                | 叶面:124 种 ARGs   | 4.43×10 <sup>5</sup> ~1.52×10 <sup>7</sup>   | 高通量实时荧光定量 PCR<br>(HT-qPCR)  | [77]              |
|               | 福建           | 施用鸟粪石的芥属植物                             | 叶面:93 种(ARGs+MGEs)  | 7.57×10 <sup>7</sup> ~5.95×10 <sup>8</sup>   | 高通量实时荧光定量 PCR<br>(HT-qPCR)  | [78]              |
| 澳大利亚          | 墨尔本          | 施用堆肥牛粪和堆肥猪粪的生菜                         | 叶面:60~61 种 ARGs<br>根内生:6~38 种 ARGs  | 7.45×10 <sup>6</sup> ~8.24×10 <sup>7</sup> /<br>4.01×10 <sup>5</sup> ~5.89×10 <sup>7</sup> | 高通量实时荧光定量 PCR<br>(HT-qPCR)  | [45]              |
|               | 美国           | 弗吉尼亚州 施用堆肥牛粪的生菜和萝卜                     | 生菜:406 种 ARGs<br>萝卜:450 种 ARGs  | —  | 宏基因组测序                      | [79]              |
| 加拿大           | 安大略省         | 施用新鲜鸡粪和堆肥鸡粪的萝卜、胡萝卜和生菜                  | <i>sulI</i> , <i>intII</i> ,<br><i>str(A)</i> , <i>str(B)</i> , <i>aad(A)</i> | —  | 实时荧光定量 PCR(qPCR)            | [80]              |

样的,既可以通过HGT作用从供体菌转移至植物受体菌,从而整合到植物微生物组中,使其具有抗生素耐药性;也可以借助ARB直接通过根际向植物组织中迁移,并定殖于其中,成为植物微生物组的一员<sup>[84]</sup>。除了常见的叶菜类蔬菜,其他种类蔬菜对有机肥源ARGs的富集作用同样值得关注。例如,MEI等<sup>[85]</sup>以块根类蔬菜胡萝卜为研究对象,发现施用猪粪有机肥显著增加胡萝卜块茎中12个ARGs和2个MGEs的生物积累量,促进10个ARGs和3个MGEs从胡萝卜表皮向内块茎转移。然而,另外一项研究指出施用牛粪或家禽粪便显著提高了樱桃萝卜根际和叶表中ARGs的丰度,但对可食用部分根系内生菌没有影响<sup>[86]</sup>。

#### 2.2.4 ARGs在土壤-水体中的迁移

降雨、径流和灌溉等活动能够加速土壤中ARGs扩散至水体系中,包括通过横向径流和垂直径流污染地表水与地下水。针对暴风雨后农田径流的研究证实,施加堆肥和粪便能够增加农田径流中*sulI*的丰度<sup>[87]</sup>。ZHANG等<sup>[88]</sup>综合评价了ARGs在不同农业土壤雨水径流中的传播特征,发现相比农田用地,果园土壤的径流具有更高多样性和丰度的ARGs,这可能是因为MGEs介导的HGT作用和微生物群落变化加剧了地表水径流中ARGs的扩散。此外,地下水中的ARGs的污染也与土壤有机肥施用有关,全球多个国家的地下水中均检测出了ARGs,其中有机肥处理土壤中的ARGs经过垂直渗漏和径流作用进入地下水是其中一个来源<sup>[89]</sup>。例如,研究人员检测发现养猪场附近井水中总ARGs和整合子(*IntI1*和*IntI2*)丰度,均显著高于无养猪场井水<sup>[90]</sup>。

#### 2.2.5 ARGs在土壤-空气中的迁移

空气中的ARGs主要以气溶胶附着的形式存在,从土壤到空气中抗生素耐药性的传播过程由自然和人为因素共同驱动,包括气候条件,风、水和动物引起的干扰与运输,以及人为施加的有机肥源ARGs<sup>[91-92]</sup>。空气中的ARGs含量一般与地面的ARGs污染程度相关,曾庆涛<sup>[93]</sup>研究发现草莓设施大棚内的空气ARGs丰度高于棚外空气ARGs丰度,土壤中的ARB负载在颗粒物上,通过风力与沉降作用进行土-气界面迁移。另一项研究在动物养殖场上方空气中检测出了丰富的ARGs,其中空气和粪便样本中ARGs与细菌群落具有显著相关性,值得关注的是ARGs在PM<sub>2.5</sub>中的富集率最高为养殖场粪便中的100倍,这表明了对于ARGs的迁移,气溶胶具有相当大的环境风险<sup>[94]</sup>。有趣的是,空气中的ARGs能够通过颗粒沉降作用影

响植物叶面的抗生素耐药性特征,在土壤-植物-空气体系中进行传播扩散。一项针对生菜叶面的薄膜覆盖实验发现通过覆盖薄膜阻断植物与空气的微生物交流,减少了生菜叶面上80.7%~98.7%的ARGs<sup>[95]</sup>。

### 3 土壤中有机肥源ARGs的环境风险评价与管控

#### 3.1 ARGs的人体暴露风险

人类活动导致有机肥源ARGs在土壤中增殖与传播,而这也使人类自己直接或间接暴露于高抗生素耐药性风险的环境中,从而对人体健康产生威胁。例如食用被ARGs污染的蔬菜与肉类,饮用被ARGs污染的地下水,或是吸入被ARGs污染的空气<sup>[96]</sup>。环境中以非致病性细菌为宿主的ARGs,能够通过HGT作用转移至人体微生物组中,当ARGs被整合入人体病原菌后,其会成为难以被药物杀死的“超级细菌”,最终引发抗生素耐药性大流行<sup>[97]</sup>。研究证实,人类肠道微生物菌群是抗生素耐药性的“储存库”,外部环境会影响人类肠道微生物组的耐药性水平<sup>[98-99]</sup>。一项研究以在养猪场实习的学生为研究对象,探究其肠道微生物组的耐药性水平随时间的动态变化,结果表明在第3个月时,学生的肠道微生物ARGs与养猪场暴露前有明显差异,其更接近于猪场工作的全职工人,猪粪和污染土壤是学生肠道中ARB的主要来源,对ARB的进一步分析说明一些导致人畜感染的致病菌也会参与环境和人体肠道微生物间传播的过程<sup>[98]</sup>。HU等<sup>[100]</sup>深入分析了3个国家的162个健康人肠道微生物组耐药性,共检出了1 093个ARGs,结果显示我国个体的抗生素耐药基因数量和丰度最高,其次是丹麦和西班牙个体;其中丰度最高的种类为四环素类抗性基因,表明人体肠道中高丰度的ARGs可能与兽药抗生素使用有关。人体肠道中ARGs的累积不仅会导致ARB的出现,还可能影响其他疾病的发生,有报道通过追踪1 200多名中老年人群糖尿病的发生与肠道微生物耐药性特征,鉴定出25个与2型糖尿病相关的ARGs,其中*vanX*、*emrE*、*ermX*和*norB*呈显著相关性<sup>[101]</sup>。

#### 3.2 ARGs风险评价方法

土壤中有机肥源ARGs能够通过多种途径在不同环境介质中传播扩散,并转移至人体微生物组中,加速抗生素耐药性危机的出现。因此,建立科学完善的ARGs风险评估方法尤其急迫与重要。研究人员提出了一项评估ARGs环境风险的规则,认为存在于

人类病原菌 MGEs 上的 ARGs 为高风险,通过新的机制产生耐药性以及不存在于病原菌 MGEs 中的 ARGs 是低风险<sup>[102-103]</sup>。ZHANG 等<sup>[104]</sup>建立了通过人体可及性(Human accessibility)、可移动性(Mobility)、人类致病性(Human pathogenicity)以及临床可利用性(Clinical availability)4个指标评价 ARGs 健康风险的方法,并对 2 561 个环境 ARGs 样本进行分析,其中 23.78% 的 ARGs 被判定为高健康风险。不同浓度抗生素残留对细菌具有不同的效应,如何能够在杀死细菌的基础上,产生小的选择压力,明确基于 ARB 的剂量-效应关系十分有必要。BEN 等<sup>[105]</sup>提出了一种剂量-效应评估方法,以大肠杆菌为耐药性研究对象,模拟实际环境条件下抗生素剂量与细菌耐药性进化的关系,从而进一步推导抗生素水平和抗生素耐药性发展之间的关系,建立致病性 ARB 和各种感染疾病之间的剂量-效应关系。

### 3.3 ARGs 风险管控策略

ARGs 的风险管控可以分为源头阻断、过程控制和末端治理 3 方面<sup>[106]</sup>。其中有机肥中 ARGs 的源头阻断主要为减少养殖业中抗生素添加剂的使用,减缓 ARB 的产生与传播。我国已经出台一系列条令和标准来限制兽用抗生素的使用,但是由于缺乏严格的监管机制与完善的技术指导,难以实现有效消减 ARGs 的目的<sup>[107-108]</sup>。过程控制主要为对动物粪便进行堆肥处理后再施用于土壤。末端治理方法为在土壤中应用生物炭材料、噬菌体疗法、电动修复和纳米材料等消减 ARGs<sup>[109-110]</sup>。

#### 3.3.1 动物粪便堆肥

堆肥是动物粪便资源化和无害化的一种有效处理方法,包括好氧堆肥和厌氧发酵,堆肥过程中产生的高温能够有效杀死粪肥中的虫卵、病原菌和杂草种子<sup>[111]</sup>。堆肥处理在降解抗生素及消减 ARGs 方面也发挥重要作用,其中 ARGs 消减主要表现为杀灭粪便中的宿主菌<sup>[112-113]</sup>。ESPERON 等<sup>[114]</sup>在堆肥 3 周后观察到 2 种抗生素减少了 23.78%,12 种 ARGs 减少了 73.7%~99.99%,潜在致病细菌或共生菌也随着堆肥过程而减少。然而随着研究的深入,人们发现堆肥对 ARGs 的消减作用有限,难以去除所有类型的 ARGs<sup>[115-116]</sup>。例如,一项研究显示堆肥对多重耐药类、磺胺类和甲氧苄啶类抗性基因没有显著影响,可能是因为这些 ARGs 具有多样的宿主菌,其中包括一些嗜热菌;此外磺胺类 ARGs 与 MGEs 协同作用,促进 ARGs 在不同宿主菌中的转移<sup>[117]</sup>。堆肥过程中 ARGs

的消减效果受多种因素的影响,包括微生物组成、重金属、C/N、pH、温度、堆肥时间和含水率等<sup>[118]</sup>。相关研究指出,在嗜热期,堆肥中的 ARGs 丰度显著下降,然而随着温度的降低,一些 ARGs (*sulI*、*sul2*、*sulA*、*drfA1* 和 *drfA7*) 丰度会增加,可能是因为短时间内一些耐热 ARGs 无法被完全去除,在堆肥后期发生反弹,表明 ARGs 的降解需要长时间暴露在高温条件下<sup>[119]</sup>。

为了解决常规堆肥过程中 ARGs 去除效率不佳的问题,研究人员提出添加调理剂优化堆肥条件,从而加速 ARGs 消减的方法。其中,超高温堆肥是指通过接种嗜热微生物,在不借助外部热源的条件下,使堆肥的温度快速提升至 80 ℃ 以上,并持续 5~7 d<sup>[120-121]</sup>。LIAO 等<sup>[122]</sup>研究发现超高温堆肥通过减少抗生素耐药质粒和相关宿主细菌的丰度,去除了 75.8% 的 ARGs 和 98.5% 的 MGEs。除此之外,先前的研究报道了多种调理剂通过影响细菌群落组成与结构,减轻堆肥中抗生素耐药性的策略,包括添加植物<sup>[123]</sup>、矿物质<sup>[124]</sup>和微生物菌剂<sup>[125]</sup>进行共堆肥。

#### 3.3.2 生物炭技术

生物炭是一种具有较大比表面积和丰富官能团的绿色多孔材料,能够有效去除环境中的多种污染物,生物炭作为土壤改良剂施用后,能够影响 ARGs 的环境行为,有效促进 ARGs 的消散<sup>[126]</sup>。生物炭消减环境中 ARGs 的主要机制为:(1)改变细菌群落分布;(2)抑制 MGEs 的产生与富集,控制 ARGs 的 HGT;(3)减少抗生素和重金属的浓度,降低 ARGs 的选择压力;(4)吸附和损坏 ARGs;(5)改变环境因素,影响 ARGs 在环境中的行为和命运<sup>[127-129]</sup>。生物炭的性质(如有机和无机组成、阳离子交换能力、pH、总表面积和孔径分布)可随原料性质和热解温度而变化,从而影响 ARGs 的消减<sup>[130-131]</sup>。为了实现对 ARGs 的高效稳定去除,一些研究对生物炭进行物理、化学和生物改性,开发出了具有出色抗菌性能的生物炭基材料。磁性生物炭/季铵盐能够通过破坏细胞膜的完整性和诱导氧化应激效应,高效杀灭和吸附去除环境中的病原微生物与游离 ARGs<sup>[132-134]</sup>。 $H_3PO_4$  改性生物炭可使堆肥中的目标 ARGs 总丰度降低 66.21%,相比之下普通生物炭仅降低了 4.02%,这可能是因为改性生物炭影响堆肥过程中细菌群落的分布<sup>[135]</sup>。ZHANG 等<sup>[136]</sup>研究发现生物炭与胡氏螺旋菌组合改性材料能够通过改变宿主菌的丰度,有效降低土壤中的 ARGs。此外,生物炭可以与超富集植物联用,协同减缓 ARGs 在重金属和抗生素复合污染土壤中的累积<sup>[137]</sup>。

### 3.3.3 噬菌体疗法

噬菌体是一类能够侵染细菌的病毒,在土壤、水、空气以及人和动物肠道环境中广泛分布<sup>[138]</sup>。噬菌体疗法通过筛选、纯化和富集得到具有ARGs宿主菌特异性的烈性噬菌体,向ARB污染的环境中加入噬菌体菌液,以达到定向侵染和裂解宿主菌的目的,从而消减环境中的ARGs<sup>[109,139]</sup>。由于噬菌体具有宿主特异性,在实际应用中常将多种噬菌体分离株组合使用,即“鸡尾酒”疗法<sup>[140-141]</sup>。针对土壤中ARGs的研究已有一些研究,ZHAO等<sup>[142]</sup>从抗生素污染的养殖场中分离获得了3种噬菌体,研究发现不同噬菌体疗法均能有效降低土壤-植物体系中ARB和ARGs的丰度,其中鸡尾酒噬菌体处理效果最好,而多价噬菌体可以维持体系中细菌的多样性和稳定性,是一种环境友好的ARGs消减技术。噬菌体还可以与生物炭联用,作为一种新型生物技术减轻土壤中抗生素耐药性风险<sup>[143-144]</sup>。研究人员发现多价噬菌体和生物炭联合使用阻碍了ARB在土壤中的垂直迁移,同时能够靶向灭活ARB,降低土壤中ARGs的丰度<sup>[143]</sup>。

### 3.3.4 其他方法

电动修复是污染场地中常见的一种原位修复手段,其原理为在电场的驱动下,污染物通过各种方式被转运到电极或某一特定位置上,从而对污染物进一步降解<sup>[145]</sup>。研究发现,在电动修复处理土壤中抗生素残留的过程中,ARB和ARGs的浓度显著降低,这可能是因为抗生素浓度减少导致了较低的选择压力,随着时间的推移,影响了土壤中ARGs的丰度<sup>[146-147]</sup>。近些年来,一些研究报道了合成纳米材料能够通过破坏细胞膜的完整性、诱导氧化应激作用、吸附损伤DNA和抑制HGT作用等方式减少环境中的ARB和ARGs,是一类具有前景的抗菌材料<sup>[148-152]</sup>。然而纳米材料并不总是起积极作用,QI等<sup>[153]</sup>将一种人造的稀土氧化物纳米颗粒加入土壤中,发现纳米颗粒暴露显著富集了土壤中约24%的目标ARGs,这可能是因为纳米颗粒促进了HGT作用,从而加速了ARGs的转移与扩增。

## 4 展望

尽管过去的研究较为全面地阐述了人为活动对土壤中ARGs水平的影响,但是环境中存在固有耐药性的背景干扰,目前的研究手段主要通过比较受人类活动影响前后的环境中ARGs水平,辨别有机肥源ARGs与固有ARGs,然而这种方法并不总是可靠的。如何准确识别并追踪有机肥源ARGs的迁移与扩散

动态,了解有机肥源单独作用,以及多种污染源协同作用与ARGs发生之间的关系是目前研究中亟待解决的问题。以后的研究有必要从以下两点开展深入研究:(1)寻找具有标志作用的环境特异性ARGs;(2)发展分子生物学技术与多学科结合的研究方法。

ARGs作为一类新型污染物,其风险特征不似传统污染物明确清晰,对ARGs环境风险和人体危害研究仍然处于比较薄弱的阶段。目前的研究很难将有机肥源ARGs的环境丰度与风险特征联系起来,也没有制定系统完善的标准和指南来评估有机肥源ARGs的环境风险。今后的研究应当加强环境中ARGs实时监测的能力,并通过建立模型的方式,评估ARGs环境暴露风险。为了明确有机肥源ARGs对人体的危害,仍需要针对以下几个不足开展深入研究:(1)有机肥源ARGs通过食物链进入人体的途径;(2)有机肥源ARGs进入人体后的传播扩散规律以及宿主菌的特征(特别关注病原体宿主菌);(3)有机肥源ARGs足够对人体产生健康危害的阈值水平。

了解环境中的抗生素耐药性风险之后,如何解决和减轻抗生素耐药性是研究的最终目的。最迫切的需求是改进畜禽养殖管理策略,减少动物粪便中ARGs的丰度和多样性,从源头控制有机肥源ARGs向环境和人体中传播与扩散。尤其是在全球范围内发展中国家和经济落后的地区,应当加强市场监管与养殖人员培训,明确抗生素添加剂的危害。应当大力开展兽用抗生素替代产品,在不损害养殖产业利益的同时,减少抗生素耐药性的发生。除此之外,针对实际土壤复杂的环境因素,研发环境友好、成本低廉、高效便捷的ARGs和ARB阻控材料与技术势在必行。

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