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Editorial

Microbiotoxicity: A call to arms for cross-sector protection of the human microbiome

Carpenter et al.'s recent study adds to the growing body of evidence showing that antibiotic use can be harmful to the human microbiome.[1] We recently introduced the term "microbiotoxicity" to describe unintended harms of antibiotic therapy to the microbiome, proposing a framework for prescribers to weigh these bystander effects against intended therapeutic benefits.[2] However, it is becoming increasingly clear that microbiotoxicity extends far beyond antibiotics, encompassing non-antibiotic pharmaceuticals,[3] dietary additives,[4] and biocide-containing consumer products.[5] Indeed, antibiotics are only one of a panoply of commonly used antimicrobials. The distinction between antibiotics, antiseptics, disinfectants, and sterilising agents lies primarily in the substrate to which they are applied: internal aspects of bodies, external aspects of bodies, surfaces, and inert substances, respectively (Fig. 1). Thus, all products with antimicrobial properties may cause unintended microbiotoxicity.

Apart from antibiotics, other pharmaceutical agents have been clearly shown to impact the microbiome, including proton pump inhibitors, metformin, selective serotonin reuptake inhibitors, statins and laxatives.[3] These drugs alter microbial diversity and function, often promoting blooms of pathobionts and antimicrobial resistant organisms. Further, dietary additives such as emulsifiers, sweeteners, colours, and nanoparticles are associated with altered gut microbiota and permeability in both animal and human studies; for instance, germ-free mouse models indicate that emulsifiers contribute causally to transgenerational metabolic syndrome and colitis.[4] Importantly, biocides are widely present in consumer products, including antiseptic soaps, chlorhexidine mouthwashes, and silver nanoparticles in clothing; these have been linked to altered microbiome and antimicrobial resistance profiles in end-users and even in treated wastewater.[5] Finally, One Health research has highlighted that antimicrobial products not only directly impact the human microbiome, but also soil, plant, and animal microbiomes, potentiating the downstream impact on human health.[6]

Like others, we have previously argued that the human microbiome satisfies many of the traditional definitions of an organ system, including predictable structure, function and ontogeny.[2] Functionally, the microbiome interacts with the endocrine, immunological, and neurological systems to maintain immune and metabolic homeostasis. We remain concerned that microbiotoxicity is strongly associated with adverse health outcomes,[2] including atopic diseases, inflammatory bowel disease, metabolic syndrome, and colorectal cancer, with compelling evidence supporting a causal relationship derived largely from animal models.[7] Although interventional human microbiome research remains limited, a causal relationship between the microbiome and human health is evidenced by the efficacy of faecal microbiome transplantation in *Clostridium difficile* infection and, to a lesser extent, ulcerative colitis and graft-versus-host disease.[8]

Given the apparent importance of the microbiome in human health and disease, harm to this organ system should be considered in assessment of toxicity associated with products intended for human use. At present, there is no requirement to evaluate the impact of novel or existing therapeutics on the microbiome, or to incorporate the growing body of microbiome research into drug licencing or summaries of product characteristics. Moreover, microbiome risk assessment is not required to demonstrate that food additives or biocide-containing consumer goods are safe for human use. There is also no requirement to show that the addition of antimicrobials to non-pharmacological products, such as textiles and cosmetics, confers health benefits. The extent to which a clinician's duty of care includes consideration of the patient's microbiome is not clear, excepting situations where there is an immediate clinical manifestation of microbiotoxicity, such as *C. difficile* infection.

The lack of formal inclusion of the microbiome in definitions of toxicity has important consequences. With no legal or regulatory mandate to document the impact of products on the microbiome, there is little incentive to perform much-needed interventional microbiome studies, or to include existing evidence in a format readily accessible to the end-user, such as drug formularies. The direct consequence is a lack of visibility of clinically relevant research, contributing to perceptions of microbiome science as 'overhyped',[9] and perpetuating its exclusion from regulation, clinical guidelines and clinical practice. The *status quo* thus impairs the ability of clinicians, patients, and the public to make informed decisions regarding the use of microbiotoxic products.

We argue in favour of an alternative approach, drawing on the Precautionary Principle adopted in environmental policy, whereby proactive risk reduction is pursued if there is plausible risk of serious or irreversible harm, even in the absence of scientific certainty.[5] We are delighted that the concept of microbiotoxicity has recently been included explicitly in a House of Lords Private Members' Bill in the UK, introduced by Baroness Bennett of Manor Castle.[10] The Consumer Products (Control of Biocides) Bill would grant the Secretary of State the power to prohibit the sale of biocide-containing consumer products intended for human use that present a danger on

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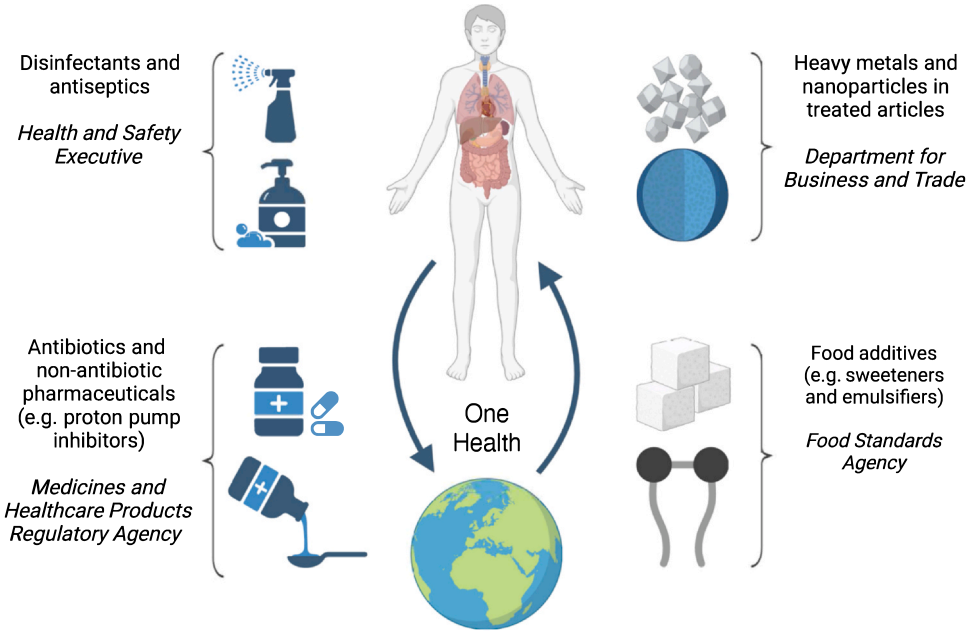

Fig. 1. Spectrum of antimicrobial products intended for human use, each of which has been associated with microbiotoxicity. Examples of UK regulatory bodies overseeing each class of product indicated in italics. Figure created using BioRender.com.

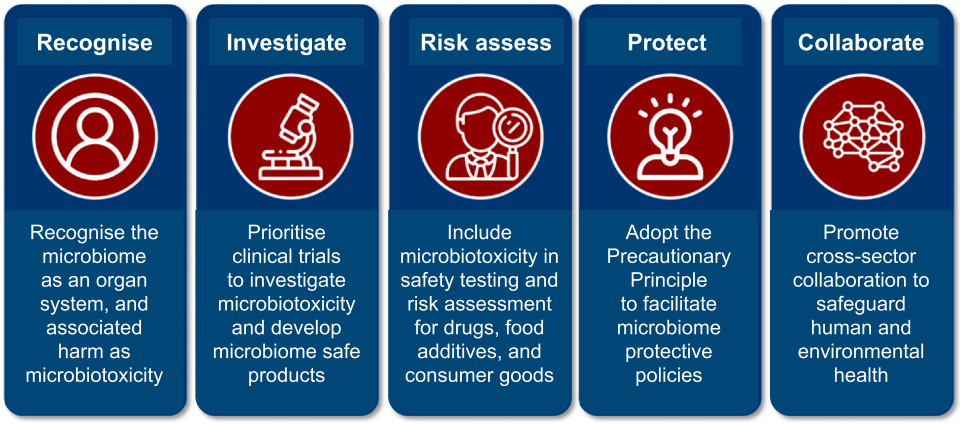

Fig. 2. A call to arms: key priorities to address microbiotoxicity.

grounds of microbiotoxicity. It would also mandate the establishment of a Biocidal Consumer Products Advisory Board to keep under review scientific and social evidence on microbiotoxicity in relation to biocidal consumer products. If enacted into law, this would provide a landmark precedent for considering the human microbiome in its own right, rather than focussing only on downstream manifestations of microbiotoxicity, such as infections caused by *C. difficile* or antimicrobial resistant microorganisms.

We echo Carpenter et al.'s warning of the limitations of inferring microbiotoxicity solely from the risk for *C. difficile* infection, and fully support their call for a more holistic approach to antibiotic stewardship. To this end, we advocate for the recognition of the microbiome as a human organ system, and for its inclusion in the safety assessment of products intended for human use, as well as in the clinician's duty of care to their patients (Fig. 2). Thus, informed use of any existing or novel product with antimicrobial properties should involve a risk assessment, in which the evidence for health benefits is weighed against potential harms, including microbiotoxicity. Cross-sector collaboration, particularly between human and veterinary medicine, public health, and environmental agencies, will be essential to address the interconnected challenges of microbiotoxicity. Recognising the microbiome as a vital organ system and prioritising its protection is not only a scientific necessity but a societal obligation to safeguard human health.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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