Food and Agriculture Organization
of the United Nations

Biocides and Antimicrobial Resistance

Summary Report of an FAO Meeting of Experts

FAO Antimicrobial Resistance Working Group

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Introduction

Within the context of One Health, the reduced efficacy of drugs to treat bacterial, fungal, and viral infections due to resistance is an increasing global concern. Divers of antimicrobial resistance (AMR) are numerous and complex. Resistance is a natural process, and resistance traits may be inherently present in microbial populations or they may be acquired by horizontal gene transfer. Such traits may be expressed under normal conditions or triggered by a number of factors, such as exposure to environmental stresses (e.g. heat, desiccation), chemicals or other biological agents. Stressors generally include drugs, chemicals, and processes used in human health care, animal health, food production, aquaculture, water treatment and environmental conditions. The prolonged or increased exposure to these stressors selects for the preferential survival of microorganisms that acquire resistance genes and allows these resistant bacteria in a population to proliferate and outcompete non-resistant organisms.

In food production, the occurrence of AMR stemming from the use of antibiotic agents in terrestrial and aquatic animal production contexts is well documented. However, the extent to which AMR is associated with the use of biocides and disinfectants – chemicals and biological agents used for the expressed purpose to control, deter, inhibit or kill harmful microorganisms – is poorly understood. For the purposes of this meeting summary, only those agents used *ex vivo* are considered as biocides, thereby excluding classical antimicrobial agents used *in vivo*.

Biocides and Resistance

Biocides are of critical importance for food safety to control microbial cross-contamination and ensure general hygiene at many stages of the food value chain. Active agents used in biocidal products include a diverse collection of chemicals that may exert a microbiocidal or microbiostatic impact through a range of different mechanisms targeting a broad spectrum of microorganisms. Some individual stressors may also co-select for resistance to multiple classes of antimicrobial drugs because of shared resistance mechanisms (cross-resistance) or genetic linkages (co-resistance) among resistance genes. If cross-resistance to antimicrobials or co-selection of antimicrobial resistance genes is driven by routine biocide use, these unintended consequences need to be evaluated and considered by relevant stakeholders (*i.e.*, manufacturers and users) and appropriately managed.

For some specific biocides, results from laboratory experiments show that exposure to particular active ingredients or biocidal products can result in increased tolerance of certain microorganisms to the active ingredient and also other antimicrobials. Examples include the use of chlorhexidine resulting in colistin resistance, or triclosan inducing isoniazid resistance. While such laboratory studies point to the possibility of cross-resistance between biocides and antimicrobials, and may provide clues

regarding factors that increase the probability of triggering antimicrobial resistance, laboratory studies do not always adequately mimic external conditions that occur under routine use. Studies investigating the development and occurrence of cross-resistance *in situ* are few and results are inconclusive.

One factor potentially contributing to the development of resistance between biocides, and potentially cross-resistance to antimicrobials, is the use of biocidal agents that rely on a narrow mode of action, *i.e.*, acting on only one or a few bacterial targets. By contrast, resistance to biocides acting on multiple bacterial metabolic pathways would require the simultaneous acquisition of resistance to these different modes of intervention to permit microorganism survival; a process that is less likely to occur than the acquisition of a single resistance mechanism. While biocides are critical tools for hygiene and food safety, they may co-select for antimicrobial resistance, therefore, stakeholders need to be made aware of this risk to have the opportunity to conduct risk assessments and implement appropriate strategies to minimize its occurrence.

Data Gaps

Further research is needed to characterize the potential risk associated with cross-resistance to antibiotics due to biocide use. Priority data gaps to address include:

(1) Studies *in situ* / in realistic conditions with biocide products and key reference microorganisms (e.g., *Salmonella*, *E. coli* O157, *Listeria*) or relevant commensals.
(2) Investigation of naturally occurring cross-resistance between biocides and antimicrobials in pathogens/commensals occurring in food production conditions.
(3) Investigations of root causes for antibiotic resistance traits found in the food value chain potentially and at least partially attributable to the use of biocides.
(4) Standardized methodologies to measure and monitor biocide resistance.

Recommended Actions

Despite current gaps in knowledge, immediate action can be taken to mitigate risk by providing clear guidance to manufacturers and users of biocidal products on practices aimed at minimizing the potential development of resistance. For instance, the use of biocides in keeping with the manufacturer's instructions and the intended product use, and validation of effectiveness specific to the application are important in slowing the development of resistance. Improper use of biocides in food production (as well as in health care, agriculture, and in the home) should be avoided as it may potentiate the problem of antibiotic resistance emergence. Examples of improper use are dilution below the working concentration and using biocide products outside their intended and validated application area. Manufacturers should provide clear instructions to users in this regard and stakeholders would benefit from education and awareness campaigns on proper usage.

Some biocides leave residues that are subsequently discharged into waste streams or otherwise contaminate the environment where they could trigger antibiotic resistance. Therefore, disinfectants that remain active even when they are washed away from food products may be less appropriate for use as biocides in food production and processing because of this potential for widespread impact on the environment and emergence of resistance. Use of technologies to inactivate residual disinfectants before introducing them into wastewater streams may be beneficial.

Manufacturers may contribute to minimizing the likelihood of antibiotic resistance developing by careful selection of active agents and formulations that target multiple bacterial sites and modes of action less likely to confer cross-resistance. In designing new biocide products, it would be prudent for manufacturers to investigate whether cross-resistance to clinically important antimicrobials is likely to occur under conditions of prescribed use. Conversely, users of biocides could be empowered and enabled to consider monitoring the potential occurrence of cross-resistance in their operations and investigate, where possible, causal links to biocide use or other triggers. Also, as our understanding of the signature microflora of food processing facilities improves, this may contribute to more optimal use of biocides in food processing environments.

As more information becomes available to fill research gaps, more specific practices to measure and mitigate the effects of biocide use on AMR development can be promoted.

Endnote

This overview of AMR and biocides is based on the discussions of a technical meeting of experts on these issues that was convened by FAO in October 2017. A more detailed technical paper is forthcoming.

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