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Biocide abuse and antimicrobial resistance—a cause for concern?

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The term biocide includes disinfectants, antiseptics and preservatives. It does not include antibiotics, which, in spite of being biocides in the strictest sense, tend to be categorized separately. In recent years there has been a trend towards use of biocides in the home environment. These products have been marketed for decontamination of food preparation surfaces (e.g. Dettox), areas perceived to be microbially contaminated (e.g. toilets) and general improvement of cleanliness in the home. A product called Microban is a biocide (triclosan) that is incorporated into chopping boards, knife handles and Wellington boots. Other companies manufacture biocide-impregnated paint (Biocote) and toilet seats. Several workers have suggested that widespread use of biocides may impact on the prevalence of antibiotic-resistant microorganisms. What is the evidence that biocide use selects for antibiotic resistance?

Biocide resistance was first recognized nearly 70 years ago by Heathman *et al.*[1] who identified chlorine resistance in *Salmonella typhi*, and antibiotic resistance was identified shortly after the availability of penicillin, but links between the two have only been recognized more recently. It is remarkable that there is a large amount of data on antibiotic resistance, with journals such as this one devoting many pages to papers describing resistance mechanisms and other journals devoted solely to the topic of antibiotic resistance. Yet there is a comparatively small number of workers worldwide who are investigating the mechanics of biocide resistance.

Because biocides tend to act concurrently on multiple sites within the microorganism, resistance is often mediated by non-specific means. Efflux pumps have the potential to act on a range of chemically dissimilar compounds and have been implicated in both biocide- and antibiotic-resistant bacteria. Cell wall changes may also play a role in the observed cross-resistance between biocides and antibiotics, probably by reducing permeability. Microbial changes that result in resistance to biocides and antibiotics should therefore cause concern. However, of equal significance, is the possibility of genetic linkage between genes for biocide resistance and those for antibiotic resistance.

McMurry & Levy[2] reported in 1998 that mutations in the enoyl reductase gene (*fab1*) of *Escherichia coli* were associated with resistance to triclosan. This work suggested that Fab1 is the target for triclosan but failed to demonstrate any significant reduction in susceptibility to antibiotics in strains with *fab1* mutations. However, the same workers have demonstrated that Inh1 (the mycobacterial analogue of the Fab1 protein) is a common target for triclosan and isoniazid in *Mycobacterium smegmatis*.[3] Thus, it is possible that overuse of triclosan may select for antibiotic-resistant strains of mycobacteria. *Mycobacterium tuberculosis*, in contrast, is known to be intrinsically triclosan resistant but usually susceptible to isoniazid, and therefore this cross-resistance may not be of relevance to the majority of clinically important infections.

Other workers have also demonstrated a link between biocide resistance and antibiotic resistance in atypical mycobacteria. Manzoor *et al.*[4] demonstrated ethambutol resistance in strains of *Mycobacterium chelonae* that had been selected *in vitro* to be resistant to glutaraldehyde. This resistance was associated with changes in the composition of the cell wall, indicating that reduced permeability may be the mechanism for this cross-resistance.

These links between biocide and antibiotic resistance are not confined to atypical mycobacteria, and it has been shown that resistance to the biocide benzalkonium chloride is closely linked to oxacillin resistance in *Staphylococcus aureus*. Akimitsu *et al.*[5] reported that benzalkonium chloride-resistant mutants of methicillin-resistant *S. aureus* (MRSA) had oxacillin MICs as high as 512 mg/L, compared with 16 mg/L for the parent strain and 0.3 mg/L for methicillin-susceptible *S. aureus* (MSSA). Furthermore, resistance to both biocides and antibiotics can be plasmid mediated. A strain of gentamicin-resistant MRSA was investigated by Yamamoto *et al.*[6] and was shown to contain a multidrug-resistant plasmid (pSAJ1) that conferred resistance to aminoglycosides, ethidium bromide, benzalkonium chloride and chlorhexidine. This plasmid, when transferred to *E. coli*, continued to express resistance to the same antibiotics and biocides as when in the original host.

Plasmid-mediated resistance to biocides is a well-recognized phenomenon. Such resistance to quaternary

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ammonium compounds and other biocides has been identified in *S. aureus*, *Pseudomonas* spp. and members of the Enterobacteriaceae, and is mediated by specific genes (*qacA*, *B*, *C*, *D* and *E*). *qacA*, *B* and *C* (described in *S. aureus*) mediate resistance by an active efflux mechanism[7] and have sequence homology with tetracycline efflux genes.[8] *qacE* is a plasmid-mediated resistance gene found in Gram-negative organisms that also codes for an energy-dependent multidrug efflux mechanism.[9] These resistance determinants are associated with resistance to a variety of antibiotics including trimethoprim, sulphonamides, oxacillin and aminoglycosides.

Perhaps the most impressive example of biocide resistance that is linked to multiple antibiotic resistance is the *mar* regulon. Strains that constitutively express the Mar protein have over 60 chromosomal genes secondarily affected,[10] and are resistant to tetracycline, chloramphenicol, triclosan and pine oil.[11] It appears that such resistance to structurally unrelated compounds is mediated by an efflux mechanism.

The public is bombarded with advertisements advocating the use of biocides in the home. The implication is that homes are dangerous places, heavily contaminated with virulent microorganisms, and the only way to ensure the safety of one's children is to use disinfectants liberally. This engenders a false sense of security in the public mind by suggesting that the widespread use of biocides reduces the organism load and thereby reduces the chance of acquiring infectious diseases. There are no data to support this stance; rather, as biocide use in the home environment as well as the healthcare environment continues to increase, the risk of selection of biocide-resistant strains must increase.

Owing to the links between biocide resistance and antibiotic resistance outlined above there is a real risk that widespread biocide use could exacerbate the already worrying trend towards increased antimicrobial resistance in clinically relevant organisms. The problem is that we do not yet know how great the problem is, or even if a problem exists. There are no good epidemiological data on the impact of biocide use on antimicrobial resistance, and our knowledge of the prevalence of antimicrobial resistance is still poor. In order to understand and control biocide and antibiotic resistance it is essential that more effort is put into surveillance so that we can understand the impact of the use of antimicrobial agents on the epidemiology of resistant organisms.

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