Biocide abuse and antimicrobial resistance: being clear about the issues

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Sir,

In a recent article in the Journal,1 Fraise considered the possible contribution of biocide use to the emergence of antibiotic resistance. As one of the few academic research groups that has maintained studies of biocide action–resistance mechanisms in their portfolio for more than two decades, we feel obliged to comment.

This article appears at a time when concerns related to the increased deployment of antibacterials in home hygiene are being raised both in the scientific and lay press. Press coverage has not disappointed in its efforts to be sensational. Not only has it been suggested that the use of biocidal products might lead to their own eventual demise, but such articles often infer that their profligate use will bring down the entire ‘house of cards’ relating to the effectiveness of antimicrobial agents and antibiotics in general. Associated with such issues is the ‘hygiene hypothesis’, which advocates that exposure to microorganisms and infection is essential for appropriate development of the immune system and suggests that we may be ‘too clean for our own good’. In consequence, measures that may reduce exposure to infection, such as hygiene and immunization, are made scapegoats for the dramatic increases in atopic disease in the developed world. Whilst we agree with the author’s proposition that profligate use of biocides in situations where infection risks are minimal is inappropriate in view of the uncertainties about potential links to antibiotic resistance, there are many situations where hygiene cannot be compromised, some of which call for use of a disinfectant product. Indeed, since the major contributor to antibiotic resistance is antibiotic use (or abuse), then appropriate and effective delivery of hygiene is now being seen as a key means to reduce the incidence of infectious disease and the antibiotic overload of our environment. Fraise suggests that the public have been erroneously led to believe that homes are ‘dangerous places, heavily contaminated with virulent microorganisms’. He fails to acknowledge that in recent years, the mechanisms of transmission of pathogens and the infection risks in the home have become much better understood. Several field and other studies, reviewed by Barker et al.2 and Bloomfield,3 demonstrate that homes represent an environment into which bacterial, viral and fungal pathogens are continuously introduced in association with food, people and pets. Such pathogens are readily spread around the home environment during normal daily activities, either directly or indirectly via hands, cloths and other surfaces, or via the air. Societal trends as reviewed by Bloomfield4 also now mean that increasing numbers of people at increased risk of infection from opportunists as well as primary pathogens are now cared for in the home by a carer who may be a family member. These various studies suggest that, through a risk-assessment or ‘targeted’ approach to hygiene, a significant proportion of the infections that occur in the home may be preventable. This mirrors infection control strategies in hospitals and other settings where the idea of producing a ‘germ-free’ environment has long been abandoned in favour of a hazard analysis critical control point (HACCP)-based approach, in which hygiene measures are targeted at high-risk sites, surfaces and activities. Whereas detergent-based cleaning, provided it is carried out with thorough rinsing of surfaces, gives some level of risk reduction, evidence from home-based studies shows that use of a product with appropriate antimicrobial properties in addition to cleaning gives an additional margin of safety by increasing the probability of achieving a satisfactory result.5–7 Application of HACCP-based principles indicates that biocide use is advisable in situations where hygiene failure carries a risk of serious consequences. This includes, for example, use of disinfectants for food contact surfaces and cloths that are used during the handling of raw foods, most particularly large surfaces and surfaces such as handles, which cannot be adequately rinsed, or surfaces such as chopping boards that are inevitably damaged during use and are difficult to ‘clean’ effectively. The recent studies by Cogan et al.6,7 show how widely Salmonella and Campylobacter are spread to kitchen surfaces during preparation of contaminated poultry and the relative ineffectiveness of detergent-based cleaning in containing the spread.

Discrepancies in the definition of the term ‘resistance’, as applied to biocides as opposed to antibiotics, has also confused the debate. Medical microbiologists rightly confine the use of the term resistance to changes in the susceptibility of a
previously susceptible organism to such an extent that it no longer responds to treatment. Erroneously small two- to four-fold changes in the MIC of biocides routinely deployed at biocidal concentrations that are 100–1000 times this level are also often referred to as resistance.8 This is particularly the case for oxidizing biocides,9 quaternary ammonium-based molecules and biguanides.10,11 The reality is that for biocides, the mechanisms that bring about cell death are generally not the same as those that inhibit growth. In practice, changes in MIC from widespread exposure to biocidal molecules are unlikely to compromise their effectiveness as bactericidal agents.12 More worrying perhaps are the changes in MICs of biocides that reflect modification of a single target or induction of efflux pumps and have the potential to confer resistance to a third party antibiotic. Whilst such cases can be speculated for groups of antibacterial agents such as the quaternary ammonium compounds and biguanides, there is currently no evidence to suggest that this has been the case.13,14 Indeed, a number of studies have concluded that in hospital environments, where arguably biocides and disinfectants have been most widely deployed over the last few decades,13 there is no consistent association between their use and the MICs of antibiotics and biocides. Two possible exceptions to this have been given a wide press; these relate to the use of triclosan and the potential selection of efflux mutants.

Triclosan inhibits the growth of bacteria through inhibition of an enoyl reductase (FabI) enzyme associated with lipid biosynthesis.15 Low-level exposure to triclosan can easily be used to select for FabI mutants of Escherichia coli that are less susceptible to triclosan.16 Arguably, since the FabI homologue in Mycobacterium tuberculosis is also the target for isoniazid,17 low-level exposure to triclosan has the potential to select for isoniazid-resistant tuberculosis. In practice, however, isoniazid-resistant M. tuberculosis retains its susceptibility to triclosan.18

Separate studies demonstrate that a major factor contributing to the susceptibility of Gram-negative and -positive bacteria to chemicals is their ability to express a wide range of efflux pumps. Expression can be induced by various factors, including low growth rate, attainment of stationary phase and sub-lethal exposure to a range of inducer molecules.19 Typical inducer molecules include not only some antibiotics and biocides, but also a range of naturally occurring substances such as spices, garlic and pine oil.20 Since the induction of efflux has the potential to empty the cell of a wide range of chemically unrelated compounds,21 including nutrients and metabolic intermediates, it is vital that cells retain the ability to limit efflux events to when they are beneficial. Efflux is therefore a responsive and highly evolved, chromosomally conserved physiological process that enables bacteria to respond to naturally occurring inhospitable environments.22 Whilst most inducers of efflux are also substrates for the pumps, some inimical agents, such as triclosan and ciprofloxacin, are substrates but not inducers. Exposure of monocultures to sub-inhibitory levels of these chemicals will therefore select for spontaneously generated efflux mutants (bulimic bacteria). Such laboratory-generated mutants often demonstrate a reduced susceptibility to some antibiotics that is theoretically sufficient to confer clinical resistance.23 Whether or not such mutant lines will be selected outside of laboratory monoculture studies, and whether the fitness cost associated with such mutations enables them to be competitive without the inimical stress, is still a matter for debate.

Although the risk–benefit debate for biocide use in the home and hospitals cannot be fully resolved in view of our incomplete picture of the scientific facts, perhaps it is time that we stop focusing so entirely on the idea that effective home hygiene means either antibacterial or non-antibacterial products, and that we become more effective in communicating what good home hygiene really means.

References


