

Biocides: health care applications

The incidence of hospital-acquired infections is used by the public as an indication of health care quality and the media is paying increasing attention to hygiene matters. The usefulness of disinfectants and antiseptics, however, is rarely mentioned. In this article, **Jean-Yves Maillard** describes how these agents work and focuses on those commonly used in health care

Biocides are non-antibiotic chemical agents used as disinfectants, antiseptics or preservatives. They kill micro-organisms or inhibit their growth. Disinfectants are agents that are applied to inanimate objects, whereas antiseptics are agents that are applied to living tissue, typically skin or mucous membranes.

The 20th century has been the golden age of biocides, with the discovery, manufacture and commercialisation of many agents. Biocides have become routinely used in domestic products, such as washing powder and washing-up liquid, various fabrics (eg, bed linen), plastics (eg, chopping boards) and even toys. This is a result of increased public awareness of hygiene and greater commercial and marketing pressures. However, with the extensive use of these agents, the following questions may be asked:

- Are biocides being used appropriately?
- What are the risks of using so many biocide-containing products?

Applications in health care

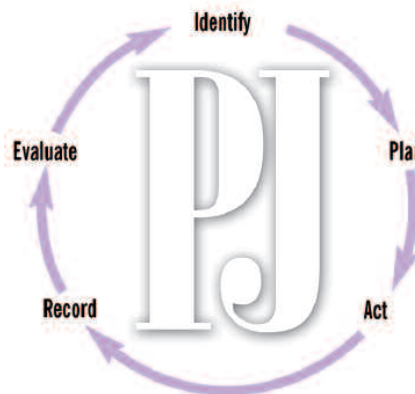
One of the main applications of biocides is to preserve pharmaceutical and cosmetic products to prevent or limit microbial contamination that can occur under normal conditions of storage and use. Preservatives include chlorhexidine, benzalkonium chloride, benzyl alcohol, chlorocresol, parabens and isothiazolinones (used in cosmetics), to name but a few.

Biocides are also used for their antiseptic properties in a number of preparations. These include products used to clean wounds, products for acne, mouthwashes, throat lozenges and sprays, and wart treatments. Panel 1 (p640) lists some biocides used as antiseptics and disinfectants. A number of natural oils are also marketed for their antiseptic properties (eg, tea tree oil is used for various skin disorders because of its bactericidal and fungicidal properties).

Biocides are applied as front-line antimicrobial agents to prevent and control infections. The reduction of hospital-acquired infections (HAIs), such as those caused by methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci, is a key government priority — reduced mortality and morbidity will decrease the overall burden on health services — and the application of biocides is an integral part of hospital disinfection policies. For example, the introduction of alcohol-based hand rubs and increased compliance with hand washing rules has been linked to a decrease in HAIs. It is now increasingly common for hospital staff to carry small bottles of alcohol-based hand rubs, clipped onto their clothes.



The introduction of alcohol-based hand rubs has been linked to a decrease in hospital-acquired infections



Identify knowledge gaps

1. What is the difference between disinfection and antisepsis?
2. List three biocides commonly used in pharmacy practice and their uses.
3. What povidone-iodine products are available?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "making a positive contribution to patients' and customers' good health" (see appendix 4 of "Plan and record").

Another application of biocides in health care includes the "sterilisation" (the term "high-level disinfection" is preferred) of heat-labile medical equipment. For example, formulations containing glutaraldehyde, ortho-phthalaldehyde, hydrogen peroxide or peracetic acid are used to sterilise endoscopes.

Biocide properties and action

Biocides are diverse in their chemical structure, properties and spectrum of activity. To ensure that they are used correctly, it is important to understand the basic requirements for activity. When used at high concentrations, biocides act at multiple targets in cells. The effect (killing or growth inhibition) usually depends on the number of sites damaged, and the extent of damage, but there are some exceptions to this rule and our understanding of the effects of biocides at low concentrations is now being questioned.

Compared with antibiotics, there is relatively little information on the interactions between biocides and microbial cells. The key requirement for activity is physical contact with the target micro-organism. This is the case with most applications, but not necessar-

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Panel 1: Examples of common biocides

Aldehydes Glutaraldehyde and formaldehyde are used as virucides in preparations to treat warts. Glutaraldehyde (2 per cent) is also used to sterilise heat-labile medical equipment but, because of its toxicity, it is being replaced by ortho-phthalaldehyde (0.55 per cent) formulations.

Peroxides Hydrogen peroxide is used to clean wounds, such as leg ulcers and pressure sores. It is usually used in 3 per cent (10 vols) and 6 per cent (20 vols) solutions or a 1 per cent cream. Hydrogen peroxide is also used in mouthwashes (1.5 per cent is used to manage mouth ulcers) and contact lens solutions (3 per cent). Formulations containing hydrogen peroxide, peracetic acid or chlorine dioxide are used to sterilise heat-labile medical equipment.

Potassium permanganate is used to clean suppurating wounds. A 0.1 per cent solution is usually prepared, which must be diluted 1 in 10 before use. Potassium permanganate has also been used for bathing by patients with infected eczema. One disadvantage of potassium permanganate is that it stains skin and clothes.

Halogen-releasing agents Povidone-iodine is available in a number of formulations, including paints, dry powder sprays, vaginal cleansing kits, pessaries and surgical scrubs. It is commonly used to treat contaminated wounds and to prepare skin surfaces for operations. However, application to large wounds or burns can result in systemic effects (eg, metabolic acidosis). Regular use can have an adverse effect on thyroid function and treatment should be avoided in patients with thyroid disorders and in those taking lithium. Similarly, iodine-containing products should be avoided in neonates. The use of povidone-iodine vaginal products should be avoided in breast-feeding women.

Sodium hypochlorite is widely used for surface and water disinfection and, with sodium dichloroisocyanurate (concentration equivalent to 10,000 ppm available chlorine), is recommended to disinfect blood spillages). Sodium hypochlorite can be used for skin antisepsis at a lower concentration (0.5 per cent available chlorine). Hypochlorite causes irritation at high-concentrations and is corrosive to metal.

Biguanides Chlorhexidine is used as an antiseptic in a large number of products, such as washes and lotions, in concentrations ranging from 0.05 to 4 per cent. Chlorhexidine is commonly used in products to clean the skin. Concentrated versions are available, which can require different levels of dilution with water or alcohol. Chlorhexidine is used to reduce dental plaque and to treat gingivitis and oral candidiasis. Regular use can cause skin sensitivity, irritation and hypersensitivity reactions (in some cases) and has been reported to reversibly discolour teeth when dental gel or mouthwashes are used. Other uses include bladder irrigation for some urinary tract infections (0.02 per cent), cleaning wounds and burns, and catheterisation.

Quaternary ammonium compounds Formulations containing cetrimide (up to 1 per cent), benzalkonium chloride (up to 0.1 per cent) or cetylpyridinium chloride are used for skin cleansing and to treat wounds and burns. Cetrimide is also included in several barrier creams and is used in combination with chlorhexidine (eg, in washes and lotions for people with acne). Development of hypersensitivity to cetrimide after several applications has been observed.

Phenolics Triclosan is a bis-phenol used in skin cleansers, antibacterial hand rubs (up to 2 per cent), dental products and products for acne. Thymol is used in mouthwashes and gargles. Its use has been hindered by its poor water solubility and reports of hypersensitivity.

Alcohols Alcohols (ethyl-, isopropyl- and phenethyl- alcohol, surgical spirit) are effective biocides at concentrations above 70 per cent. They are used to prepare the skin for injections or venepuncture. Alcohols are mostly used in combination with other biocides, notably in alcohol-based hand rubs.

Information compiled from Martindale 2002 and the British National Formulary 2004

ily for biocides incorporated or embedded in plastic, fabrics and other materials, where the biocide has to be released, or moisture is needed, to ensure activity. When a biocide is in contact with the cell, it can interact at the outer cell layer, the cytoplasmic membrane and in the cytoplasm (see Figure p641).

Limitations The efficacy of biocides, regardless of their use, is affected by a number of factors. However, these are often not properly understood or ignored by users, and dramatic reductions in efficacy are possible. Factors can be divided into those related to the biocide, those related to the micro-organisms and those related to the product or object to be treated (see Panel 2).

Concentration is, by far, the most important factor. At high concentrations, and when all other conditions are optimal, biocides will kill most micro-organisms, including fungi and viruses. The effect of dilution on biocidal activity can be predicted by calculating the concentration exponent (η). Biocides with a high concentration exponent (eg, phenolics and alcohols) will rapidly lose activity on dilution. Those with a lower concentration exponent, such as cationic biocides (eg, chlorhexidine), are less affected in this way.

Contact time is also important and standard guidelines usually recommend a minimum contact time for specific applications (eg, one minute for hand washing with a surgical soap is recommended).

Ignoring the contact time can allow microbial survival and using biocides at incorrect concentrations could contribute to the selection of resistant micro-organisms. There have been many reports of contaminated biocidal formulations resulting from inappropriate use, such as "topping up" with water, which decreases the effective concentration. Glutaraldehyde-resistant *Mycobacterium chelonae* have been isolated from endoscope disinfectors as a result of a drop in concentration below 2 per cent.

Soiling (eg, serum, blood, pus, food residues, faecal materials, etc) can decrease biocidal activity, either by mopping up the agent or by offering some protection to micro-organisms, or both. Cleaning before disinfection is, therefore, paramount. This is particularly applicable when the item or surface to be disinfected is highly contaminated (eg, bronchoscopes).

Temperature might be of concern in terms of preservative efficacy. A decrease in temperature is usually associated with a decrease in activity, so care is needed with storage of preserved pharmaceuticals at a low temperatures.

Poor availability decreases efficacy. The availability of a biocide can present a problem in formulations where there is partitioning of the agent into an oil or aqueous phase, and in tablets, where the water availability is low, the effectiveness of biocides is limited, since water is essential to ensure contact between the biocidal molecule and the micro-organism.

Biocide efficacy also depends on the type of micro-organisms present, although this can be difficult to predict in practice. Among the most resistant types of micro-organism are bacterial spores (which are used as biological indicators for sterilisation processes), then mycobacteria, protozoal cysts and non-enveloped viruses. Micro-organisms found in environments where growth conditions are poor are usually less susceptible to biocides.

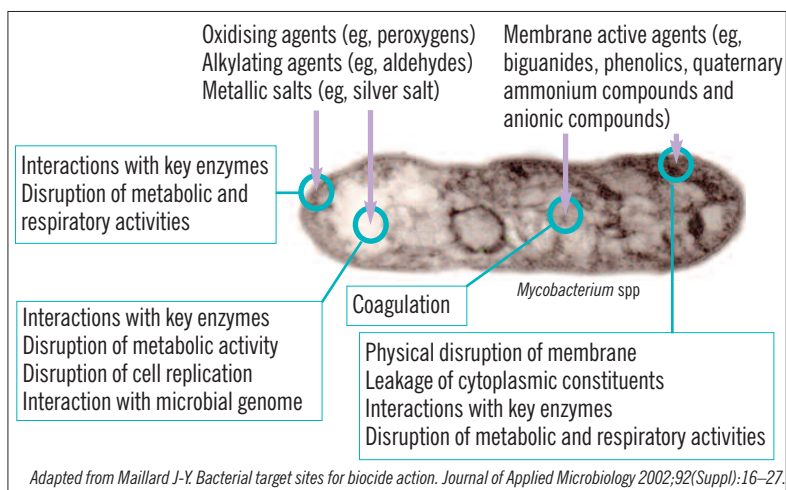


Figure: Examples of biocide interactions with a bacterial cell

Bacteria often grow as a biofilm (ie, a microbial community) rather than separately. Within a biofilm, most bacteria will have a low metabolic activity (due to restriction to nutrients, oxygen etc) and such micro-organisms have been described as far more resistant to biocides as well as to some antibiotics.

Measurement of activity There are a number of recommended international protocols for evaluating biocide efficacy. Numerous studies, particularly those investigating the emergence of bacterial resistance to biocides, rely on measurements of the minimum inhibitory concentration (MIC). Although useful to identify susceptibility trends, such studies are not so applicable to practice (eg, in health care and the food industry), and testing for lethality, rather than inhibitory activity, is recommended. Standard methods involve demonstrating that a percentage of micro-organisms are killed within a set time and under specific conditions (eg, concentration, organic load, pH, temperature,

Dramatic reductions in efficacy are possible if biocides are not used correctly

etc). The suspension test, which involves mixing a known concentration of a micro-organism with a biocide in solution, is commonly used to demonstrate simple antimicrobial activity. More advanced tests attempt to mimic conditions *in situ* (eg, hand washing tests).

The British Pharmacopoeia describes, in detail, an efficacy test for preservatives.

Resistance Some degree of resistance has been reported to almost all biocides in laboratory studies. Bacteria, in particular, have developed multiple defence mechanisms which aim to decrease the concentration of the biocide to a level that will allow their survival and growth. Defences include an “impermeability barrier”, which decreases the amount of biocide that can penetrate the cell, efflux pumps and detoxifying enzymes that decrease the intracellular concentration of a biocide. Some resistant determinants, for example, encoding for an efflux pump, can be transferred between bacteria. The modification of the target site, a common mechanism responsible for antibiotic resistance, has only been reported on rare occasions with biocides, notably with triclosan.

Multiple-antibiotic resistant micro-organisms (“superbugs”) are not necessarily less susceptible to biocides than their antibiotic-sensitive counterparts. However, the possibility of bacterial cross-resistance between biocides and antibiotics has been raised in the scientific community. This has not been reported in the media because there is a lack of information about the meaning, extent and consequence of such resistance in practice.

Selection

The perfect biocide does not exist (see Panel 3, p642). Selection of a biocide should depend on its intended use, the characteristics of the agent (eg, toxicity, corrosiveness, spectrum of activity) and the conditions of application (eg, the degree of risk a particular surface presents, the types of micro-organisms expected, soiling and level of microbial contamination).

When choosing a biocide (and the concentration it is to be used at) as an antiseptic, or as a preservative in products that will be in contact with tissues, toxicity must be considered. Most biocides show some toxicity at the concentrations used and contact dermatitis and sensitivity reactions (eg, with chlorhexidine) have been reported. In addition, some biocides are corrosive (eg, hypochlorites) and this limits their use on some surfaces.

It is difficult to recommend one antiseptic or disinfectant over another because of the number of formulations available for a specific application and the various factors affecting efficacy. In addition, comparative efficacy studies are relatively rare. However, knowing the type of agent present in a product will give some indications of its efficacy and likely adverse effects.

Inappropriate selection of biocides as preservatives in pharmaceutical preparations could result the survival and growth of micro-organisms and lead to spoilage and possibly

Panel 2: Factors influencing biocidal activity

Biocide factors

- Concentration
- Soiling
- pH (affects the ionisation of the molecule and, therefore, activity)
- Contact time
- Temperature

Micro-organism factors

- Type of micro-organism (eg, spores, viruses, fungi, cysts, bacteria)
- Number of micro-organisms (large populations are more difficult to inactivate)
- Phenotype (biofilm formation can alter the expression of genes, causing resistance)
- Metabolic status (dormant bacteria are less susceptible than actively growing bacteria)
- pH (pH affects surface charge of the organism and microbial growth)

Product/object factors

- Surface type (eg, porous surfaces can protect micro-organisms)
- Water activity (low water activity [eg, in tablets], decreases biocide efficacy)
- Hard water (the presence of ions can impede biocidal activity)
- Relative humidity (some biocides are more active at high relative humidity)
- Preparation constituents (some constituents can neutralise the biocide)
- Type of material (some biocides are absorbed by plastics or rubbers)
- Type of formulation

infection (if a contaminated preparation is administered or used). The choice of an appropriate preservative has to be a balance between retaining high efficacy and low toxicity.

Other considerations

There are currently diverging opinions as to the indiscriminate use of biocides in health care. Some scientists advocate the use of biocides for non-critical surfaces, although others are more cautious in their recommendations. Indeed, some surfaces might only need cleaning and do not require chemical disinfection because they are rarely heavily contaminated, whereas other articles need thorough cleaning with detergents before chemical disinfection. Some institutions rotate the use of biocidal formulations, although there is a lack of evidence for the benefits of this practice.

Improvements in hygiene have been advocated to combat the spread of HAIs but the implementation of such measures is often less than satisfactory. Disinfection policies should take into account the level of disinfection required and should be easily implemented in practice.

A further argument is that the indiscriminate use of biocides will impact on the environment because many compounds are toxic and not readily degradable. There is also a possibility that the extensive use of biocides might create a false sense of security and lead to the non-observance of basic hygiene rules.

The number of biocidal formulations or products is likely to rise because of marketing pressures and better informed consumers, as well as the benefits of reducing HAIs. The European Biocidal Product Directive makes the introduction of novel molecules difficult (high costs are associated with the development of a new biocidal molecule) so it is likely that new products will be based on potentiation of activity and improved delivery of existing agents. Activity could be potentiated through the combination of biocides, or biocides with enhancers. Although not new, this offers interesting prospects, including specifically targeting mechanisms involved in bacterial resistance or virulence. As for improving delivery, the use of polymer technology should help enhance the release of lethal doses of biocides from medical devices and provide the possibility of releasing a biocide on demand.

Disinfection, antisepsis and preservation efficacy could also be improved through formulation (enhanced activity) but improving compliance is also important.

The use of biocides needs to be balanced between the clear benefits of controlling infection and the potential risks associated with use, not only in terms of emerging microbial resistance, but also toxicity and environmental pollution. There is no doubt that biocides will continue to play an important role in the prevention of infections. However, biocide manufacturers need to be further involved in training end users. Training nursing and domestic staff on the various factors affecting efficacy (eg, to ensure that basic hygiene is not overlooked) would increase the effective use of these agents.

Panel 3: Properties of an ideal biocide

- It has a wide spectrum of activity
- It is microbicidal at a low concentration and acts rapidly, notably on surfaces
- It should not be neutralised or quenched easily (eg, by hard water or organic load)
- It is non-toxic and degradable
- It causes minimal damage to products or surfaces
- Costs should be acceptable and supplies assured

The need and benefit for novel applications should be appropriately evaluated and they should not be used solely as a result of commercial pressures. Appropriate surveillance programmes should also be put in place to monitor efficacy, but also microbial susceptibility.

This article has dealt mainly with bacteria, for which more information is available. Other pathogenic micro-organisms such as viruses, fungi and protozoa are often overlooked and more information is needed about the efficacy of biocidal products against these organisms.

Resources

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Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Examine the range of povidone-iodine and chlorhexidine products and make sure you know how each should be used.
2. The section on disinfectants and preservatives in Martindale includes information on contact lens care, disinfection in Creutzfeldt-Jakob disease, hepatitis and HIV infection, and injection site and catheter care. Read the introduction to this section and find the answers to the following questions:
 - Should skin be disinfected before injections?
 - What advice should be given to travellers to countries where water is not disinfected at source?
 - Which biocide is particularly useful for preventing acanthamoeba infections?
3. Are biocide-containing products for domestic use effective or a commercial ploy? The usefulness of antiseptics on broken skin has been questioned — according to Martindale, antiseptic solutions are “of doubtful value”. Discuss with a colleague.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?