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Sterilisation techniques for polymers

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Abstract: The effect of terminal sterilisation techniques on medical polymers is diverse. Few sterilisation agents are without adverse effects on polymers: heat (steam and dry heat), radiation, ethylene oxide, ozone, hydrogen peroxide. Heat can alter, damage, degrade, distort and expand heat-sensitive polymers. Ethylene oxide is toxic and can leave toxic residues. Hydrogen peroxide and ozone can absorb, affect the gloss of, discolour and oxidise some polymers. Radiation can degrade, destroy and change molecular structures of some polymers. This chapter considers not only chemical and physical effects of sterilisation techniques, but also some effects on applications, biocompatibility and device compatibility.

Key words: biocompatibility, comparative efficiencies, polymers and sterilisation.

7.1 Introduction

Sterilisation techniques are fundamental to the preparation of polymers into sterile medical devices and hospital products. Polymers are the most widely used class of materials in biomedical devices, but they may be sensitive to various sterilisation techniques. Finding the correct polymers for medical devices or biomaterials requires serious consideration regarding design, processing and performance, including biocompatibility, functionality and the effect of sterilisation. The effect of sterilisation on polymers is a key factor in device design.

For example, device designs with thick and dense absorbing polymers may absorb larger quantities of toxic ethylene oxide (EO) residues or hydrogen peroxide, and limit the penetration of hydrogen peroxide, steam and less penetrable electronic-beam (e-beam). Unfortunately, there is no singular sterilisation technique panacea for 'all' polymers and implantables. Consequently, polymer compatibility to sterilisation technique is a major concern, and is the focus of this chapter. As part of the manufacture process for a device, the impact of the sterilisation technique on the final biocompatibility and functionality of the device must be evaluated. Both the product biocompatibility and physical and functionality properties provided must be validated through the intended shelf-life of the device.

Manufacturers should be selective in their choice of polymers for components and devices. They should also be aware of how polymers may interact with various tissues, particularly during long-term implantation. Concern for polymer compatibility will ultimately offer longer life cycles and better cost-effectiveness for the user.

7.1.1 Sterilisation techniques and their effects on polymers

There are few techniques capable of sterilising polymer products. Factors to consider when selecting a technique include the fact that steam or dry-heat sterilisation could degrade or melt some plastics. EO leaves toxic residues; hydrogen peroxide and oxidising agents can oxidise or damage some materials. Radiation can alter the molecular structure of many polymers (by cross-linking or scission), cause odours and discolouration, embrittle and degrade some materials, affect bond strengths and cause changes to shelf-life. Consequently, the effect of sterilisation on medical materials and polymers provides reasons why one technique is employed and why another is not considered. However, being suited to more than one sterilisation technique will improve the accessibility of a device. What techniques are acceptable and available for medical polymers and devices will determine the sterilisation method(s) of choice.

Most sterilisation techniques, except for EO, involve harsh treatment that results in adverse physical and chemical effects, including molecular changes that may not be visible, affecting mechanical properties, functionality, safety and toxicity.

7.2 Dry-heat sterilisation

Dry-heat sterilisation may be as simple as baking but is often more complex. It is used for sterilising oils, petroleum jellies, surgical catguts and instruments, glassware, including vials for pharmaceutical drugs, and silicone prosthesis and other medical devices. It is also used in sterilising dental instruments to minimise corrosion of sharp items and in laboratories for depyrogenation of glassware, where other techniques are not able to destroy pyrogens. Dry heat is frequently used as part of aseptic processing in the pharmaceutical industry. It is also the method of choice for spacecraft sterilisation, and for sterilising electronics boards, ceramics and other moist heat-sensitive materials and products.

Dry heat can sterilise most heat-resistant polymers, as can steam sterilisation, but it can also sterilise moist heat-sensitive polymers. Steam and dry heat have many similarities, including ease of control and monitoring, low

cost and the absence of toxic residues or wastes, as may occur with EO or radiation. Steam and dry heat are less expensive than EO and radiation processing.

Some other dry heat applications include the following:

- Silicone implants that are sterilisable. They are cross-linked by radiation, impermeable to steam or absorb peroxides and EO.
- Sterilisation of dry chemical-containing devices that would otherwise be destroyed by moist heat, EO, radiation or oxidising agents.
- Sterilisation of electronics components which are damaged by steam, high humidity, EO/formaldehyde or irradiation. Radiation-sensitive materials, such as acetal, polypropylene (PP), silicone and Teflons®, are good candidates for dry heat.
- Polyurethanes (PUs), which are hydrolytically attacked by steam or degraded by radiation, are good candidates at low temperatures.
- Sterilisation of contrast medium at extremely high temperatures (e.g. 190°C), but with extremely short exposure times (e.g. 6–12 min).

Some temperature–time relationships for dry heat sterilisation are shown in Table 7.1.

A disadvantage of dry-heat sterilisation is the long time required to heat up and cool down. The transfer of (dry) heat is relatively slow and, particularly for polymers, requires removing significant moisture and sterilisation of contact areas at elevated temperatures for extended exposure times.

Table 7.1 Temperature–time relationships for dry heat sterilisation

Temperature	Time (overkill)
330°C	1.15 s
190°C	6 min*
180°C	30 min†
170°C	60 min†
160°C	120 min†
150°C	180 min (3 h)
105–135°C	Overnight (e.g. >8 h) or longer†
88°C‡	4–5 days

Notes: Time chosen depends on load size, mass and configuration, time to penetrate and the degree of overkill. Lesser times may be chosen based on bioburden control, resistance and improved heating methods.

* A Cox steriliser uses forced heat air at 2500 ft/min to heat. Infrared irradiation can heat materials more quickly.

† Exposure times vary with equipment, circulation, loading and cool down.

‡ Dry heat below 100°C may be possible but requires additional moisture removal from microbes, dehydration (desiccation) and low bioburden to be effective.

Overcoming stratification of temperature and difficult to penetrate areas (e.g. joints and mated surfaces) is critically important. Heat is an effective process for heat-tolerant polymer materials and devices, many of which have been designed to be resterilised. Implantables are not typically resterilised in practice, although a few may be.

Dry heat is recommended only for those materials, such as certain glass containers, oil, powders, some polymers (e.g. acetals, silicone, Teflons®), where it is undesirable to use steam.

7.2.1 Effects of dry heat on polymers

Dry heat can distort, melt, soften or expand many polymers. It requires higher temperatures for the same cycle or exposure time as steam sterilisation, or longer exposure times at steam temperatures. With expertise, the longer dry cycle or exposure times may be significantly reduced. Under such circumstances, dry heat may be more compatible with more heat-tolerant or moisture-sensitive polymers than steam.

Polymers can only be sterilised by dry heat below their melting, transition or degrading temperatures. Polymers and materials compatible with dry heat sterilisation (low and high temperatures) are diverse (see Tables 7.2 and 7.3). Heat sterilisation can be harsh on polymers, requiring elevated temperatures for complete inactivation of heat-resistant spores and particularly for prion inactivation (e.g. >300°C). However, good control of bioburden can allow for lower dry-heat inactivation temperatures (e.g. 105–135°C).

Dry heat cannot sterilise aqueous liquids, only non-aqueous substances (e.g. oils) per se. Consequently, steam is a better technique when it comes to sterilising aqueous solutions within heat-tolerant polymers. However, dry heat may be applied as part of the drying and cooling phase of the steam process. Compared with steam, dry heat does not involve limited penetration (silicone is non-hydroscopic), moisture sensitivity of some polymers and post-sterilisation wetting problems. It can sterilise acetals, PP up to 120°C and Teflons® (e.g. FEP, PCTFE) up to 170°C; irradiation would damage and embrittle these polymers.

Heat sterilisation, whether by dry heat or by steam, can cause thermal degradation of polymers and this may be due to oxidation. Thermal degradation of polymers involves molecular deterioration as a result of overheating. At high temperatures, the components of the long-chain backbone of the polymer begin to separate (molecular scission) and react to change its properties. Thermal degradation provides an upper limit to the service temperature of plastics, as does the possibility of mechanical property loss. Indeed, unless correctly prevented, significant thermal degradation can occur at temperatures much lower than those at which mechanical failure is likely to occur. Consequently, plastics or polymers selected for heat

Table 7.2 Polymer compatibility to dry heat and steam sterilisation techniques

Polymer	Comments (vary – consult authors or suppliers)
Acrylonitrile butadiene styrene (ABS)	Very unlikely, but some may be poor to possible, depending upon grade, filler Run low temperature process
Fluoropolymers	
Polytetrafluoroethylene (PTFE)	Compatible up to 170°C or higher Certain grades may allow for several cycles or long service; however, although PTFE has great thermal stability, once the activation energy for the rupture of the C-C bonds in the chain has been exceeded, it can unzip quantitatively releasing a potentially toxic monomer
Perfluoroalkoxy copolymer (PFA)	Working temperatures up to 204°C or higher Long term up to 170°C
Poly chlorotrifluorethylene (PCTFE)	Up to 150°C continuous
Polyvinyl fluoride (PVF)	Heat deflection temperature up to 134°C; limited use
Polyvinylidene fluoride (PVDF)	Per use temperature is 150°C (302°F); however, some grades may only go to 125°C Multiple, maximum operating temperature of 275°F/130°C
Ethylenechlorotrifluorethylene	Compatible to 266°F (131°C); melt at 412°F (211°C)
Ethylene tetrafluoroethylene (ETFE)	Up to 150°C
Fluorinated ethylene propylene (FEP)	Up to 170°C or 200°C (392°F)
Polyoxymethylene (e.g. polyacetal)	Up to 121°C or higher; may degas May use up to 100 cycles at 121°C, but it may begin to degrade, emitting formaldehyde
Polyacrylic (e.g. PMMA)	Poor to fair; some highly resistant grades
Polyamide (e.g. Nylon)	Poor to excellent Absorbs moisture, some films will allow moisture to diffuse through
Polycarbonate	There are grades that can be sterilised at 134°C Some formulations only allow a few cycles; other formulations allow up to 200 repeat cycles

(*Continued*)

Table 7.2 Continued

Polymer	Comments (vary – consult authors, or suppliers)
Polyester	Possible to excellent; depends upon type, grade, form and function Some good PET films at 240°F, PEN good Mylar resistant but will not allow steam penetration Aliphatic polyesters sensitive are to hydrolysis, while aromatic polyester (e.g. PET) may be less susceptible
Polyethylene (PE) – various densities; LDPE, LLDPE, HDPE, spun polyolefin®	Poor to fair HDPE fair and spun polyolefin fair High density better than low density Reinforcement of HDPE improves its temperature
Polyimides (PI)	Possible to excellent; depends upon grade, form and function PEI withstand up to 4000 cycles 1000–2500 at 5 min @134°C
Polymethylpentene (PMP)	Excellent up to 235°C; PMP withstands repeated autoclaving, up to 150°C
Poly (ether) Ketone	High temperature resistance; PEEK has heat resistance Good up to 2000 h of steam Typically long service
Polypropylene	Depends upon grade, form and formula Use heat-resistant gradewith heat stabiliser for multiple cycles
Polypropylene copolymer (PPCO)	It is autoclavable; provides properties of polypropylene and polyethylene PPO replaces polyallomer
Polystyrene	Standard polystyrene not autoclavable; but syndiotactic polystyrene (S-SPS) is excellent, as is styrene
Polyphenyloxides (PPO)	Good, 215°C; can be mixed with styrene
Polysulfones	Typically all types are excellent; however, polyether sulfone (PES) is less resistant Repeated autoclave cycle – PS up to 1500 cycles; but not PES
Polyurethane	Poor/possible, but some grades may be fair/good
Polyvinylacetates	Depends upon form, function, formulation and co-polymerisation. Heat-stable PVA hot-melt adhesives used
Polyvinylchloride	Rigid PVCNL, but possible with modifiers; plasticised PVC good depending on form, formulation and function

Styrene acrylonitrile copolymer (SAN)	Possible to fair; depends upon grade
Silicone	Has tremendous heat resistance, but is not a barrier to moisture vapour; dry heat may be better in some applications. If exposed to repeated steam sterilisation will eventually relax silicone and will become gummy
	Silicone is hydrophobic, it will resist moisture
	Diffusion, unless nano-channels exist
Thermoset polymers	
Epoxy reinforced plastics	Numerous types of reinforced epoxies
	Physical properties can vary. Heat distortion temperatures of up to 470°F
Phenolics	Autoclaving can lead to phenolic degradation and extractable into fluids
Polyester, unsaturated	There are a variety of unsaturated polyesters (e.g. vinyl esters). C better cross-linked.
	Possible to good
	Isophthalic acid-based polyester
	High-temperature resistance
Polyimides (e.g. BI maleimides (BMI) and acetylene terminated polyimide (ACTP))	BMIs and ACTP have use-service temperatures of 127–232°C and 316°C
Polyurethane (PU)	Typically possible; depends upon grade, form and function. There are heat-resistant cross-linked polyurethanes
Aliphatic	Radiation cross-linking increases its resistance
Aromatic	Aromatic thermoset PUR does not form 4,4′-methylenedianiline (MDA) in polyurethane
Adhesives	
Acrylic	Can tolerate autoclaving; depending upon grade and formulation, fair to good
	There is an acrylic adhesive film in a tape up to 280°F
Epoxy	Depending upon grade and formulation, deflection temperature from 200 to 500°F
	Some can lose retention of initial strength on only five cycles
Fluoroepox(y)ies	Epoxy adhesives; depending upon cure and formulation, good to excellent
	Epoxy adhesives cured with heat are more heat resistant than those cured at room temperatures

(*Continued*)

Table 7.2 Continued

Polymer	Comments (vary – consult authors, or suppliers)
Silicone adhesives	Typically good; depends upon form, formulation and function, good to excellent Some may be good for only up to 6–8 cycles
Elastomers	
Butyl	Good,depending upon type and grade Resistant to water and up to 120°C Multiple use – a halobutyl(halogenated poly (isobutylene))
Ethylene propylene diene monomer (EPDM)	Good up to 125°C in water; up to 134–150°C in air; continuous-use operation; temperature of 105°C
Natural rubber-latex (synthetic cis 1–4 polyisoprene)	Possible to fair There are autoclavable grades Plastomers enhance thermal stability. Possible to fair Hardens with use Withstands repeated autoclaving at 250°F for 20 min
Nitrile rubber (acrylonitrile butadiene)	Good resistance to moisture and water Tolerate temperatures of up to 120°C at lower processing conditions, below 230°F Better if hydrogenated nitrile rubber
Polyacrylic	Polyacrylate: it is a heat resistant rubber; water resistance can be improved but with decrease in heat.Typically, resistance to water is poor.
Polychloroprene	Fair resistance to moisture, up to 230°F; intermittent to 250°F Fair to very good It is possible to resterilise at below 230°F
Silicone elastomer	There are some representative polymers for steam sterilisation technique
Styrene block copolymers, SBR	Depends upon grade, type, form and formulation Possible to fair It is possible to resterilise up to 100°C

Thermal-based polyisocyanate, urethane (polyether/polyester)	There are some heat-resistant grades; depends upon type, form and formulation With silicone there is increased heat resistance Not likely to be multiple sterilisations
Thermoplastic elastomer (TPE)	Polyolefin that can be moulded into autoclavable parts
Urethane elastomer aliphatic	Typically possible; some up to 135°C. Steam autoclaving possible with selected grades
Urethane elastomer aromatic	Formation of 4,4′-methylenedianiline (MDA) with steam

Sources: AAMI TIR 17[1] and references 2, 3 and 5.

sterilisation should be reviewed for their transition temperatures as well as melting temperatures. The chemical reactions involved in thermal degradation may lead to physical and optical property changes relative to initially specified properties. Thermal degradation generally involves changes to the molecular weight (MW) and MW distribution of the polymer and property changes include reduced ductility and embrittlement, chalking, colour changes, cracking and a general reduction in desirable physical properties. (Note: Radiation also involves changes to MW and MW distribution, but oxidative radiation can also cause cross-linking.)

7.2.2 Adaption of dry heat to minimise effects on polymers

The main disadvantage of dry heat is its elevated temperatures, which are not compatible with many materials and polymers, but it becomes more effective at lower temperatures (e.g. 121°C vs 170°C). Where there is a need for rapid sterilisation, dry heat is often lacking, having a long cycle or exposure time. However, with the addition of chemical or physical agents the heating time of polymers and products may be drastically reduced. Common time–temperature relationships for sterilisation with dry heat are shown in Table 7.3. To enable spacecraft sterilisation, lower dry-heat sterilising temperatures were established. Spacecraft sterilisation can be performed in the range 105–35°C. The possibility of sterilisation below 100°C (e.g. 66–88°C), but at extremely long exposure times under dry/desiccated conditions, was also discovered.

At these lower temperatures and longer exposure times, more polymers can be adequately sterilised with fewer degrading effects on their properties than with steam sterilisation. Dry heat sterilises polymers without the hydrating, moisturising and wetting of steam (which may cause hydrolysis of some bonds, etc.). At lower temperatures, dry heat may sterilise as many, if not more polymers than moist -heat sterilisation, because of corrosion, hydration, hydrolysis or wetting of certain materials. However, the extended heating time for dry heat sterilisation may cause a gradual softening or distortion of certain materials (e.g. polyvinyl chloride, PVC); this may require reducing any load on PVC. A longer cycle, lower temperature and integration of heat lethality during the heating and cooling steps can be used to avoid polymer or product degradation. Knowledge of the rate of polymer degradation or decomposition and the kinetics of bioburden death rate at different temperatures enables optimisation of cycle parameters. Improving heating up and cooling down with dry-heat creates a total cycle time that may be shorter than a total EO cycle with preconditioning and aeration.

Table 7.3 Polymers and materials compatible with dry-heat sterilisation technique (low and high temperatures)

Acetal (ACL), delrin, or polyoxymethylene up to 121°C (dry)
Aluminum up to 190°C (dry)
Cellulose acetate (non-load) up to 120°C
Cellulose acetate butyrate (non-load) up to 130°C
Cotton muslin up to 204°C
Glass >190°C
Grease (depends upon the type of grease) (dry)
Ethylene chlorotrifluoroethylene (ECTFE) up to 150°C
Epoxies (vary up to 177°C)
Ethylene propylene diene monomer (EPDM) up to 149°C
ETFE up to 150°C
Ethylene acrylic 149°C
Fluorocarbon rubber 199°C
Fluorinated ethylene propylene (FEP) up to 170°C
Fluoro silicone 232°C
High-density polyethylene (HDPE) up to 120°C
Hydrogenated nitrile rubber 149°C
Liquid crystal polymer (LCP) up to 275°C
Metals (note some metal temper may occur above 160°C) up to 190°C (dry)
Muslin up to 160°C
Natural rubber 104°C, but low heat ageing resistance
Neoprene/chloroprene rubber 121°C
Nitrile rubber 100°C, and low heat ageing resistance
Nylon 4/6 (polyamide heat-stabilised grades) up to 130°C
Nylon 6 <100°C
Paper (varies depending upon paper) up to 160°C (dry)
Perfluoroalkoxy (PFA) up to 170°C
Petrolatum gauze up to 160°C
Phenolics (vary) up to 150°C
Polyacrylate (ACM) 149°C
Polycarbonate (PC) up to 134°C
Polyetherimide up to 134°C
Polyetherketone (PEI, PEEK, etc.) up to 170°C
Polyethylene (vary per molecular weight (e.g. 80–142°C))
Polyethylene terephthalate copolymer (PETG) up to 170°C
Polyimide 232°C
Poly 4-methyl-pentene-1 (PMP) up to 170°C
Polypropylene (PP) up to 135°C, no stacking
Polyphenylene oxides (PPO) 100–148°C
Polypropylene copolymer (PPCO) up to 120°C
Polysulfone (PSF) up to 160°C
Polytetrafluoroethylene (PTPE) up to 170°C
Polyvinyl chloride tubing (flexible-non-load, varies) up to 120°C
Polyvinylidene fluoride (PVF) up to 125°C
Styrene-butadiene rubber 100°C, but heat ageing resistance
Silicones up to 200/232°C
Teflons® up to 170°C
FEP up to 170°C
PFA up to 170°C

(*Continued*)

Table 7.3 Continued

Select a polymer whose temperature transition or melting temperature is comfortably 'above' the required, selected or chosen dry heat sterilisation operating temperature. Melting and/or deflection/maximum temperature can vary with formulation changes.

Note: Polymer responses may vary with the length of exposure to a temperature.
Sources: AAMI TIR 17[1] and references 2, 3 and 5.

Since dry-heat sterilisation involves not only elevated heat but also removal of moisture or desiccation of microbes, additional means to improve moisture removal and microbe desiccation will significantly shorten required exposure time, but a case by case decision is usually required.

Increased temperatures and rapid microbe dehyrdation will result in shorter inactivation times. However, the time to heat up and cool down will be longer for shorter exposure times. Consequently, the total process time may be an adjustment of heat-up, exposure time and temperature, and cool-down to optimise the process. Since it is easier to achieve lower temperatures, particularly with low heat transfer of polymers, reduced temperature dry-heat processing may be optimal. For *in situ* produce and aseptic assembly sterilisation with minimum or no packaging, efficient loading for heating may improve heat-up time as well as the time to penetrate and sterilise.

Cycle and exposure time depends on load, penetration time and the validation approach used. Load, mass or stress affect a material during dry-heat sterilisation and some materials may soften and flatten as a result of direct contact with other items in the load.

Choosing a polymer involves selecting a material that best fits the dry-heat process and temperature of choice. The number of polymers that can be dry-heat sterilised has increased (see Tables 7.2 and 7.3). As the sterilisation temperature and microbial moisture decrease, the heat-up and cool-down periods of the cycle also decrease.

Polymer selection begins with consideration of heat deflection, glass transition, melting and/or optimum operating temperatures. Heat stability can be enhanced by the addition of heat stabilisers to the formulation. Dry-heat sterilisation is useful for polymers that are adversely affected by moisture, hydration (e.g. ethylene vinyl acetate (EVA)) or cross-linking (silicone). For example, some transparent plastics that absorb small amounts of water vapour and appear cloudy after autoclaving are ideal candidates for dry-heat sterilisation. Conversely, materials are not 'easily' heat sterilisable – for example, acrylonitrile–butadiene–styrene (ABS), acrylics, polystyrene and low-density polyethylene (LDPE) – can be damaged by exposure to high temperatures. Dry-heat sterilisation of silicones is preferable because

radiation causes cross-linking; EO creates too many toxic residues and many techniques fail to sterilise intrinsic oils and other materials, where humidity cannot be diffused.

7.3 Steam (moist heat) sterilisation

Steam sterilisation can be as simple as using a pressure cooker, but is often more complex. It is a traditional method used in hospitals and laboratories where reusable materials and products are frequently resterilised. Pharmaceutical companies use it for sterilising heat-resistant drug solutions and it is also used in decontamination of infectious waste. The method is limited to use with heat-tolerant, moisture-resistant polymers. Compatibility with high temperatures and moisture resistance is necessary for moist steam cycles. Steam is compatible with aqueous liquids and can sterilise most metals, glass and a large number of heat-resistant plastic materials. The number of materials compatible with steam varies considerably with the sterilisation temperature.

Steam sterilisation is often performed at temperatures of 121–34°C. However, processing temperatures of moist-heat sterilisers may range from 105°C to 150°C. In saturated-steam processes, the processing temperature corresponds to a saturated-steam pressure significantly above atmospheric pressure.

Operating and process pressures used in steam applications cover a wide range, depending on the type of process required. Processes might use high vacuum levels to eliminate air, while exposure pressures range from a low of 3 psig for a low-temperature process to as high as 70 psig for air overpressure, water-spray and water-immersion processes. The latter processes are generally used to maintain the integrity of the polymer, shape of the container and compensate for the pressure created by the increase in temperature.

Cycle and exposure times vary with temperature and with heat-up and cool-down times. The rate of product heating should be controlled to minimise the possibility of differential expansion. The cool-down phase of a cycle can be a critical period in which polymers, packaging or containers burst or distort with change in internal pressure versus external pressure, and requires a positive pressure overlay. A longer heat-up and cool-down phase typically reduces the exposure time required. Heat-up time enhances the heating of material. Cooling time reduces heat and eliminates moisture from the steriliser.

Time–temperature relationships[2] for steam sterilisation include:

- 3 min 134°C* pre-vacuum for immediate to use or flash sterilisation;
- 18 min 134°C* pre-vacuum for reduction of prion activity;
- 12–15 min 121°C* pre-vacuum or not for immediate to use sterilisation;
- 30+ min 121°C* for wrapped instruments, trays or liquid bottles;

- 60 min 121°C* for reduction of prion activity;
- 120 min 121°C immersion in 1N NaOH for sterilisation of prions;
- 30–40 min 115°C*.

*Exposures vary depending upon:

- load density,
- heat capacity,
- configuration,
- heat-up,
- cool-down time,
- time to penetrate,
- overkill approach versus bioburden.

Lesser times may result based upon bioburden control and resistance, and integration of time/temperature during heat-up and cool-down steps.[2]

Standard steam sterilisation is carried out at 121°C for 15 min. Processing temperatures can be reduced to 110–15°C, depending on the bioburden, device design and heat resistance of the polymer. With recent emphasis on the environment and toxicity, ease of sterilisation of the cotton mould *Pyronema domesticatum* and sterilisation of prions, there is renewed interest in steam and its compatibility with the environment and health and safety. Immediate use (or flash) steam sterilisation continues to be a process for use with pre-vacuum cycles; however, it can be applied to pre-vacuum, high vacuum and steam-flush-pressure-pulse sterilisers and different cycles (i.e. gravity-displacement and dynamic air removal).

Flash steam processes should not be used for:

- implants, except in a documented emergency situation when no other option is available;
- post-procedure decontamination of instruments used on patients who may have Creutzfeldt-Jakob disease (CJD) or similar prionic disorders;
- devices or loads that have not been validated with the specific cycle employed;
- devices manufactured and sold sterile and intended for single use only.

Note: Flash steam sterility can be improved with appropriate tray covers or other barriers to items being sterilised, which eliminate or reduce contamination by environmental microbes. Flash steam sterilisation achieves a higher degree of inactivation of highly resistant thermophilic biological indicator spores for equivalent process conditions compared with liquid sterilisation. Liquid-sterilised items are more vulnerable to recontamination,

require drying and offer less barrier protection than flash sterilisation. The latter is also a just-in-time (JIT) approach. Speed (i.e. JIT) and aseptic handling both reduce the opportunity for contamination.

7.3.1 Effects of steam sterilisation on polymers

Unlike dry heat, with steam sterilisation not only is there potential thermal degradation and decomposition of a polymer but also the potential for hydrolysis. Some polymers lose structural integrity at temperatures used for autoclaving. Products made from such polymers may need to be supported to prevent distortion. Polymers where the softening temperature is higher than the autoclaving temperature may suffer from the release of moulded-in stresses and subsequent distortion. Where steam sterilisation is to be used, the effect of multiple cycles needs to be considered to prevent cumulative effects when the product is single-use disposable. If the products are packaged before autoclaving then packaging material and method need to be carefully chosen. The suitability of packaging for steam sterilisation will depend on the polymer, the size and wall thickness of the package and the contents, including any sharp corners, which may pierce the package. Polymers suitable for steam sterilisation are listed in Table 7.2.

The number of polymers capable of tolerating moderate temperature and moisture (steam and/or heated water) is more numerous than often considered:

- Natural (isoprene), ethylene propylene diene monomer (EPDM), urethane, nitrile, butyl and styrene-butadiene rubber.
- Fluoro plastics (other than PTFE and FEP) – that is, PVDF, PCTFE, PETFE.
- 'High-end' engineering resins, PEK, PEEK, polyetherimide.
- Nylons (polyamides), especially aromatics, 12, 11, 6/12 and 6/10.
- High-density polyethylene (HDPE) and UHMWPE.
- Polycarbonate (PC) and alloys.
- Polyesters (e.g. PET and PETG), but aliphatic forms are vulnerable to hydrolysis.
- Polysulfone (PSF) and polyphenyl sulfones.
- PVC; flexible and semi-rigid, colour, plasticiser and HCl corrected, where no load is involved.
- Syndiotactic polystyrene (S-PS); SAN can also be heat resistant.
- Some PUs.
- Polypropylene (stabilised), copolymers (PPCO) and polymethylpentene (stabilised).
- Thermosets – epoxies, phenolic, polyimides, PUs, aromatic polyesters.
- Silicones.

For details of the effects of steam sterilisation on these polymers, see Table 7.2. Resistance of polymers will depend on formulation, additives and stabilisers.

Unlike most other methods, steam is compatible with liquids (including drugs which are packaged in polymers) or filters that sterilise drsugs. Plastics transfer heat more slowly than metal and so it may take longer to reach sterilising temperatures in the autoclave. Because of differences in heat transfer characteristics between plastics and inorganic materials, the contents of plastic containers may take longer to reach sterilisation temperature (e.g. 121°C). Therefore, longer autoclaving cycles are necessary for liquids in large-volume plastic containers. Adequate cycles can be determined only by experience with specific liquids and containers.

Improvements in computer controls, monitoring devices, loading, biological and chemical indicators have paved the way for renewed applications of this technology, and the growing need for more compatible materials. Improvements in polymers for steam sterilisation are being made with addition of heat stabilisers, copolymerisation and improved polymerisation with metallocenes, pelletisation and moulding temperatures. Note: A metallocene is a compound – for example, consisting of two cyclopentadienyl anions ($C_5H_5^-$) bound to a metal centre (M (e.g. iron)) in the oxidation state II, with the general formula $(C_5H_5)_2M$. Closely related to the metallocenes are the metallocene derivatives – for example, titanocene dichloride and vanadocene dichloride. Metallocenes generally have high thermal stability.

The thermal and chemical (steam) degradation of polymers are closely inter-connected, as also are biological and chemical mechanisms. Thermal degradation of polymers by steam is similar to that described for dry heat (see Section 7.2.1), but with the addition of hydrolysis mechanisms. Thermal degradation may involve environmental stress, cracking and plasticiser migration and loss. Steam-induced chemical reactions include oxidation and hydrolysis, which result in particular problems.

Steam sterilisation can cause thermal degradation of polymers and this may be due to oxidation. The thermal degradation of polymers has already been described for dry-heat sterilisation. For example, the thermal oxidative degradation of polycarbonate may begin up to 150°C. Thermal decomposition of a polymer is the chemical decomposition caused by heat. The reaction required to break the 'chemical' bonds in the polymer undergoing decomposition is essentially an oxidative process. For example, some polyesters are somewhat resistant to steam sterilisation, but aliphatic forms are more vulnerable to hydrolysis than the aromatic form. Oxidative degradation may occur in PET at temperatures as low as 100°C; however, the ester bonds in aliphatic PET are prone to hydrolysis and the permanent use of the material in steam above 70°C should be avoided. Some PU formulations are very vulnerable to steam sterilisation because of moisture swelling of the material.

7.3.2 Adaption of steam (moist heat) sterilisation to minimise effects on polymers

Sterilisation techniques may significantly affect the properties of polymers, including their suitability for implantation. Under some conditions, a technique thought to be compatible with a polymer will not be suitable when tested. This incompatibility is often due to changes in process parameters, environment or due to additives that reduce corrosion. For example, the high-temperature flash steam process under vacuum may affect a polymer differently than the low-temperature gravity steam method. The lower temperature will be less harsh on the polymer than the high-temperature flash process.

While polymers can be selected based upon melting temperatures that exceed processing temperature, lower steam sterilisation temperatures can also be implemented so that polymers will become more stable over time (heat-resistance ageing). Polymers with lower melting temperatures can be used as possible future considerations include alternative or combination approaches to lower steam sterilisation temperature. For example, dialysers can be steam sterilised in place (SIP) on carousels and released in a JIT fashion through process controls and parametric release. These dialysers can also be sterilised with liquid water at high temperatures. Many pharmaceutical/healthcare plastic containers, such as high-density polyethylene, PVC and Polyallomer (a copolymer of propylene and polyethylene (PE)) filled with liquids can be steam sterilised at temperatures lower than 120°C. Steam sterilisation can be reduced, however, to as low as 105°C, depending on the bioburden, device design and heat resistance of the polymer material. Lower steam temperatures may be considered with use of acids or certain chemical additives.

Combining steam sterilisation with other sterilising or enhancing physical or chemical agents can further reduce sterilisation temperatures suitable for polymers with lower melting temperatures. For example, a steam–formaldehyde sterilisation method operates at 65–85°C. This approach could be applied to steam with EO or propylene oxide (PO), resulting in a preservative by-product such as propylene glycol for PPO that may be beneficial for incorporation in some biomaterials. An acidic medium for steam heat allows for reduced or lower sterilising temperatures below 100°C. High-density materials are typically more resistant than low-density materials (e.g. PE); except when the physical state of steam (vapor) is changed to heated (liquid) water.

Some miscellaneous concerns regarding steam sterilisation are the following:

- Some chemical additives (e.g. anti-rust agents) in steam will attack transparent plastics and cause a permanently glazed surface after autoclaving, or leave toxic residues after drying and removal of steam and moisture.

- Some transparent plastics (e.g. PVC) may absorb minute amounts of water vapour and appear cloudy after autoclaving. The clouding will disappear as the plastic dries. Clearing may be accelerated in a drying oven at 110°C. For PVC tubing, clearing is obtained at below 75°C for upwards of 2 h.
- Use of polypropylene copolymer (PPCO) bottles may be preferred instead of polysulfone with Tween in the autoclave.
- Steam sterilisation of PUs may result in formation of toxic leachable 4,4′-methylenebisphenyldiamine (MDA); however, a mixture of PU and polysilicone may result in acceptable biocompatibility.
- PP mixed with PE may result in an acceptable heat-tolerant copolymer (e.g. polyallomer or polypropylene copolymer).

In most situations, moist heat sterilisation temperatures are too high to allow many low temperature-tolerant polymer and biomaterials to function properly after high-heat sterilisation. However, since temperature is a useful tool for evaluating the shelf-life of many polymers, it is important to monitor potential changes in polymers or product functionally and performance in the life of an implantable. Also, consideration of sterility entity may be a concern with this technique, where it is sometimes more surface (e.g. silicone prosthesis) than penetrable.

7.4 Ethylene oxide (EO) sterilisation

Ethylene oxide (EO) is a traditional method that is able to sterilise many polymers, including heat-sensitive polymers, but not liquids. It may craze some polymers and it can leave toxic residues and by-products if not handled correctly. The EO technique has some penetration capabilities, but requires a long time for the overall process (e.g. preconditioning, sterilising and aeration). EO is an effective and soft sterilant for most reusable medical materials, polymers and devices. It is used in both hospitals and industrial manufacturing applications for manufacture of disposables.

Common limitations of EO sterilisation relate to diffusion barriers, process time and interactions. Diffusion barriers limit the efficacy of EO sterilisation if the EO gas, temperature and humidity necessary cannot penetrate into all locations within a device – for example, into a stopcock, a very long, thin lumen or large, dense product load. Long overall process times can be an economic limitation to the application to EO due to long preconditioning periods, extended exposure times, post-sterilisation aeration times and post-processing biological indicator testing. While parametric release is difficult to achieve uniformly with this method, faster release times can be achieved with the use of rapid biological indicator incubation times.

Hazardous material handling and toxic residues are issues since EO is an explosive, potential human carcinogen and reproductive toxicant. It requires gas mixtures or special handling, robust scrubbers for gas emissions and significant consideration of worker exposure.

7.4.1 Effects of EO sterilisation on polymers

EO sterilisation is compatible with nearly every polymer, except those that may be particularly sensitive to humidity, low temperature and high EO gas concentrations. EO sterilisation is very gentle with most polymers, and used wisely. Some polymers compatible with the EO technique are listed in Table 7.4. EO is compatible with nearly every polymer; if there is a problem with the polymer because of the technique, there often is an expert solution. EO can sterilise many polymers that can not be irradiated or heat sterilised.

Some of the limitations related to EO may be due to a polymer's absorptivity towards accumulating residues, but this will vary significantly with humidity, EO gas concentration, temperature and aeration. There may be some sensitivity to humidity – for example, for hydrophilic coatings – but there are usually solutions to this problem. Users also need to be careful with EO sterilisation when using polymers as carriers for drug delivery. Drugs such as Taxol-based formulations cannot withstand high-temperature and high-humidity EO cycles.

Although EO will sterilise most polymers and materials for medical devices, because it is a potential human carcinogen and reproductive toxicant, its use is limited and controlled. Post-sterilisation evaluation for toxic residues (e.g. ethylene chlorohydrin) must be performed before release or validation of product. Long exposure and post-sterilisation aeration times, as well as post-processing biological indicator testing, may make the process less practical.

Because it is a gentle process, there is virtually no polymer degradation per se with EO. There may be some effects due to humidity and EO gas carriers (e.g. Freons). If temperature, gas, pressure or humidity effects are high, there are ways to alter these parameters to eliminate their effect.

7.4.2 Adaption of EO sterilisation to minimise effects on polymers

A potential way of lowering EO cycle times, as well as reducing toxic residue levels, is to increase the sterilising temperature from 45–60°C to 70–80°C, as used with the steam–formaldehyde process. The higher temperatures drive EO and ethylene chlorohydrin residues towards ethylene glycol, which is not

Table 7.4 Some polymers compatible with the ethylene oxide technique

Thermoplastics	Effects
Acrylic	Good. Some loss in tensile properties, no discolouration reported on multiple cycles with HCFC-124/EO blends There may be some crazing Excellent with low EO/CO_2 concentration gas mixture, except at high sterilising temperature >63°C. Low EO cycle with EO/CO_2 gas mix had low absorbency and very short aeration
Acrylonitirile butadiene styrene copolymer (ABS)	Compatible High absorbence of EO and long aeration for desorption Excellent with low EO/CO_2 concentration Gas mixture with low EO concentration had low absorbance and short aeration
Non-plasticised polyvinyl chloride (PVC)	Compatible EO/CO_2 concentration Gas mixture with low EO concentration had very short aeration
Plasticised polyvinyl chloride (PVC)	Compatible Plasticised EO absorbs more than non-plasticised PVC Excellent with low EO/CO_2 concentration Gas mixture with low EO concentration had very short aeration
Polyacetal	Compatible, no degradation Low EO concentration with EO/CO_2 gas mix had short aeration
Polyamide (Nylon, all classes)	Compatible Increased residuals with high humidities; but low residuals with low EO concentration with EO/CO_2 mix
Polyarylsulfone	Compatible
Polycarbonate	Compatible. Some formulations may be subject to stress cracking and some loss of tensile properties after multiple cycles and an extended time post-processing, no discolouration
Polyether sulfone	Compatible
Polyetheretherketone (PEEK)	Compatible
Polyethylene (PE, UHMWPE, LDPE, LLDPE, HDPE)	Generally compatible. HDPE may lose some tensile properties, no off-gassing Excellent with low EO/CO_2 gas concentration mix; absorbs and desorbs EO well, very short aeration EO is excellent with UHMWPE for hip and knee implantation
Polyethylene terephthalate glycol copolymer (PETG)	Compatible

Polymethyl methacrylate (PMMA)	Compatible, no discolouration; EO acceptable for contact lenses
Polyphenylene oxide	Compatible
Polypropylene (PP)	Compatible. May be some long-term effect on tensile modulus. Excellent with 100% EO. Good with HCFC, no brittleness
	Can sterilise unstablised PP in syringes with no brittleness
	Excellent for 100% (pure) ethylene oxide gas. Good for HCFC-124 blend. Excellent with EO/CO_2 gas mixture
	Absorbs and desorbs EO well
Polystyrene	Typically poor. Some embrittlement and loss of tensile strength for some formulations has been reported
	However, polystyrene petri dishes have been easily sterilised (excellently) with EO/CO_2 gas mixtures and with moderate humidities; many European IV sets with styrene were compatibile with polystyrene parts
	Polystyrene tissue ware will absorb EO and will not desorb well enough
	For cell culture growth, unless low EO concentration in EO/CO_2 gas mix. No crazing and no residuals with low EO concentration with EO/CO_2 gas mix
Polysulfone	Compatible
Polytetrafluoroethylene (PTFE)	Compatible
Polyvinyl chloride	Compatible. Rigid PVC may decrease impact resistance after exposure. Medical-grade plasticised tubing may contain significant residual levels until aerated
	EO/CO_2 gas mixtures had little EO residuals with low EO concentration
	EO and CO_2 have the same molecular weight
Styrene acrylonitrile copolymer (SAN)	Generally OK for one cycle, but may embrittle and lose tensile properties on multiple cycles. May exhibit surface cracking and stress cracking on multiple cycles. Standard EO cycles have high EO absorbency and poor desorption, requiring long aeration
	Compatible with low EO/CO_2 gas concentration. Low EO concentration cycle with EO/CO_2 mix; had low EO absorbency and very short aeration
Styrenic block copolymer	Compatible
Polyester	Compatible
	With low EO concentration, EO/CO_2 mix had low EO absorbency and very short aeration time

(*Continued*)

Table 7.4 Continued

Thermoplastics	Effects
Polyetherimide (PEI)	Depending on formulation and application. Very thin tubing may present compatibility issues. Bulk structural materials are generally compatible
Polyurethane	Performance depends on formulation, cure conditions, material thickness and end use stresses. PU has high affinity for EO but releases with aeration
	Low EO concentration with EO/CO_2 gas mix had short aeration
Silicone (RTV)	Excellent; no cross-linking
Butyl rubber	Butyl is even stable in liquid EO
Ethylene propylene diene (EPDM)	Generally compatible, but changing curing method to sulphur cure from peroxide cure may result in formation of small amounts of polyethylene oxide inside the matrix of the material
Latex	Compatible, but may be limited to the number of repeat cycles
Neoprene®	Compatible
Polyvinylidene fluoride elastomer	Compatible
Silicone elastomer	Compatible; no cross-linking
	High absorbency or EO desorbs well for short aeration with low EO concentration
	EO/CO_2 mix had low EO absorbency, and very short aeration
	Non-elastomer prosthesis requires long aeration at high EO concentrations; but at very low EO concentrations with EO/CO_2 gas mixtures, EO residuals may be much lower
Teflons®	Good to excellent materials.There may be low EO absorbency, but very slow desorption in some types (e.g. PTFE), but not in PVDF. Low EO concentration in EO/CO_2 mix may result in very little EO absorbency

Note: EO residuals will vary between polymer types, polymer designs, thickness, formulation changes, packaging, etc. Typical aerations vary between 2 and 7 days.The above very short aeration was <12 h at ~50°C with initial low EO concentration with EO/CO_2 gas mixture.
Sources: AAMI TIR 17[1] and references 2 and 3.

toxic according to ISO 10993-7. Ethylene glycol is not as significant a residue as EO and ethylene chlorohydrin. Since the higher temperature and moisture at 70–80°C create more ethylene glycol, residues are not such a significant problem. Improvement of plastics with heat stabilisers and copolymerisation enhances the number that can be sterilised at these slightly higher temperatures.

Preconditioning of some polymers (e.g. cuprophane) allows EO sterilisation to be performed without in-vessel humidification of this moisture-sensitive dialysing material. EO sterilisation requires aeration and ventilation of toxic residues to minimum acceptable levels before medical devices or biomaterials are releasable. Heat, gas aeration/exchange, vacuum and time all help to remove EO residues.

EO may be used to sterilise many implantables. However, the complex matrices of many polymeric devices might result in high EO residue levels or the process may alkylate or hydrolyse chemically reactive molecules during implantation. While EO may be excellent for many implantables, the high cost of setting up validating chambers, process monitoring, environmental management, hazardous materials training, protective clothing, risk managements, EO recovery and additional regulatory paperwork, added to the operating costs, making it unattractive. Potential or possible changes in polymer or product functionally and performance over the life of the implantable must be monitored and evaluated.

7.5 Low-temperature hydrogen peroxide with plasma

Hydrogen peroxide (H_2O_2) has excellent microbiocidal properties, but poor penetration, yet is environmentally acceptable when controlled. H_2O_2 is typically used in the vapour phase for medical materials and devices. While compatible with many polymers, there are some materials that are damaged (e.g. acrylics, cellulosics (including paper), natural rubbers and bioadsorbables, such as polyglycolides and polyesters). It does not have the same penetration as pressurised steam, dry heat, EO or irradiation and is principally a surface sterilant.

It can sterilise somewhat short lumens, but cannot sterilise some polymeric materials and devices in their entirety. While its outcome is usually safe, sterilisation begins with a source of very hazardous highly concentrated H_2O_2. Plasma breaks down the H_2O_2 into water and oxygen. Because H_2O_2 has very high vapour or boiling point, very deep vacuums are required that may adversely affect some packaging and materials. Sterilisation is typically achieved in small vessels, not the large chambers or facilities used with dry heat, EO, radiation or steam.

7.5.1 Effects of H_2O_2 sterilisation on polymers

H_2O_2 and oxidising agents can sterilise a multitude of polymers. Some polymers compatible with H_2O_2 with plasma are listed in Table 7.5. The number of polymers is more limited than EO because of the oxidising effect of H_2O_2. However, it is more attractive than EO sterilisation because of its

Table 7.5 Compatabilities of some polymers with hydrogen peroxide (with plasma*)

- ABS (excellent)
- Acetal – significant colour changes or slight material changes after 10–100 cycles. Grade dependent
- Elastomers – silicones (excellent), thermoplastic polymer elastomer (TPE) (styrenic block copolymer compounds (SEBS), thermoplastic elastomer 'Q' polymer (TPQ)), natural (degrade), EPDM (fair to good), urethane (grade dependent), nitrile (good, grade dependent), butyl (excellent), styrene-butadiene (excellent), polyacrylic (good), polychloroprene (excellent)
- Fluoroplastics (PTFE and FEP, PVDF, PCTFE, PETFE) – excellent
- PEK, PEEK, polyetherimide (excellent, no change after 100 cycles)
- Nylons (polyamides), absorb, severe material degradation after 10–100 cycles. Grade dependent
- Polyethylene, LDPE < LLDPE, HDPE, UHMWPE (excellent, no change after 100 cycles)
- Polyesters (PE) and PETG – excellent
- Polycarbonate (PC) and alloys – excellent
- Polysulfone (PSF) – excellent
- Polyvinyl chloride (PVC) flexible and semi-rigid, colour, plasticised (good no resterilisation)
- PVC unplasticised (some colour change or surface changes after 50 cycles)
- Polyurethane (8 chemical varieties) – some colour change or loss of gloss after 100 cycles; however, polyurethane is a peroxide absorber and this can lead to decomposition of the peroxide needed for sterilisation
- Polypropylene (unstabilised) – excellent
- Polypropylenes (stabilised) and copolymers (PPCO) and polymethyl pentene – excellent
- Polystyrene and copolymers, ABS, PS, SAN – excellent
- Polyacrylics (PA, PMA, PAN) – grade dependent; significant material changes or crazing after 10–50 cycles
- Silicone – excellent, no change
- Thermosets – epoxies, phenolics, polyimides, polyurethanes, polyesters (grade dependent)
- Acrylic – fair, resterilisation not likely

Note: *Material compatibility with hydrogen peroxide vapour sterilisation may not be the same as that with low-temperature hydrogen peroxide with plasma.

Sources: AAMI TIR 17[1] and references 1, 3 and 5.

shorter process time and lack of residuals. Its very short processing time and absence of carcinogens make H_2O_2 very accessible. When designing devices, it is best to avoid absorbers, such as PU, nylon, EVA and cellulosic.

Low-temperature H_2O_2 with plasma has less effect on polymers than H_2O_2 vapour without plasma, because plasma destroys more peroxide residues than with aeration. Plasma and oxidising agents are generally applied only to small niche and minimal-sized devices. It is used predominantly in general hospitals, and less so in medical device manufacture. As a surface sterilant it may not be suitable for implantables.

7.5.2 Adaption of H_2O_2 sterilisation to minimise effects on polymers

Variations in sterilisation techniques may significantly affect the properties of polymers, including their suitability for implantation. Additionally, under some conditions H_2O_2 sterilisation, which is generally thought to be compatible with a polymer, may not be suitable when tested. This incompatibility is often due to small changes in process parameters, the environment or due to the formulation/stability of the sterilant or polymer. A reduction in H_2O_2 concentration will improve the compatibility of some polymers, as well as reducing processing temperature.

The highest MW materials (with the narrowest MW distribution) should be used for most applications. H_2O_2 treatment of implantables might require special processing, but it can sterilise UHMWPE used in knees, hips and shoulders. Concerns over oxidation and plasma effects, and its predominant surface nature, mean H_2O_2 with plasma has not been frequently applied to implantables. However, it is worth considering contacting equipment manufacturers for specific applications. Biocompatibility according to appropriate standards should be established for implantables, regardless of sterilisation technique selected.

7.6 Ozone sterilisation

Ozone is a very strong oxidiser, making it an effective and efficient sterilising agent. It is a relatively new technique for medical devices, although it has been used to sterilise water, etc. In vapour form, ozone can be used to sterilise medical products and other materials within a chamber. Because ozone is metastable, it cannot be stored and is therefore produced *in situ*, making the process safe and environmentally acceptable. At the end of the process, the ozone is degraded to oxygen. Because of the strong oxidising nature of ozone, materials must be resistant to oxidation. The main disadvantage of ozone includes its reactivity with certain polymers. It also has some penetration limitations (e.g. through organic matter and non-diffusible polymers).

A number of polymers are now sterilisable using ozone (see Table 7.6). Ozone sterilisation has recently been introduced to healthcare facilities. There are no toxic residues and it is more penetrable than H_2O_2 vapour (with plasma), but not as penetrable of polymers or devices as EO, steam, dry heat or irradiation.

In gaseous low-temperature ozone sterilisation, the process parameters include vacuum, time, temperature, ozone concentration, humidity and pressure. The ozone concentration is typically 85 mg/L for 15 min at 30–36°C. The process temperatures are generally low, making it suitable for temperature-sensitive materials.

Table 7.6 Some representative polymers sterilisable with the ozone technique

- Elastomers – silicones (peroxides and platinum cured), TPE (SEBS, TPO), natural (isoprene), EPDM, urethane, styrene-butadiene, butyl and natural rubber – are not likely materials
- Fluoroplastics, PTFE and FEP, PVDF, PCTFE, PETFE
- 'High-end' engineering resins, PEK, PEEK, polyetherimide
- Nylons (polyamides), especially aromatics, 12,11, 6/12 and 6/10, but some changes may occur after multiple cycles
- Polyacetals – OK, but some colour change and loss of gloss may occur
- Polyethylene, LDPE < LLDPE, HDPE, UHMWPE
- Polyesters (PE) – unsaturated polyesters are excellent
- Polycarbonate (PC) and alloys
- Polysulfone (PSF)
- Polyvinyl chloride (PVC) – flexible and semi-rigid, colour, plasticiser and HCl corrected
- Polyurethane (8 chemical varieties) – may be poor
- Polypropylenes (stabilised) and copolymers (PPCO), and polymethyl pentene that is radiation stabilised; otherwise unknown
- Polystyrene and copolymers, ABS, PS, SAN
- Polyacrylics (PA, PMA, PAN)
- Thermosets – epoxies, phenolics, polyimides, polyurethanes, polyesters – may vary

Sources: AAMI TIR 17[1] and references 1 and 3.

7.6.1 Effects of ozone sterilisation on polymers

During ozone sterilisation, ozone breaks down into reactive species, including hydroxyl radicals and atomic oxygen. Because of the strong oxidising nature of ozone, polymers must be resistant to oxidation. Polymers and medical devices should also be resistant to high relative humidity levels (>80%), which are required for ozone to be effective. Consequently, materials should be resistant to oxidation and moisture. The method cannot be used for fluids or woven textiles. Although many polymers may be satisfactorily used in the manufacture of a device intended for single use, they might not be effective for use with a reusable or refurbished device.

Polymers compatible with low-temperature ozone sterilisation are listed in Table 7.7. The compatibility of some polymers with ozone remains unknown. Woven materials, polystyrene, PU, butyl and natural rubber, and polychloroprene are unlikely to be compatible. Some cellulosics, however, may be compatible. The shape of a device as well as its design may be closely related to its stability and resistance to sterilisation. Device and polymeric parts with wide surface-to-mass ratios (e.g. fibrous materials) can undergo faster oxidative degradation. While such devices and materials are for single use or used in the manufacture of a device that has limited reuse, such a condition might not be satisfactorily used for a device with a longer expiration

Table 7.7 Compatibility of some polymers for ozone sterilisation technique

Thermoplastics	Compatibility	Number of cycles polymer may be compatible
Fluoropolymers		
Polytetrafluoroethylene (PTFE)	Excellent	No change after > 100 cycles
Perfluoro alkoxy (PFA)	Excellent	No change after > 100 cycles
Polychlorotrifluoroethylene (PCTFE)	Excellent	No change after > 100 cycles
Polyvinylidene fluoride (PVDF)	Excellent	No change after > 100 cycles. PVDF is considered a polymer of choice for ozone
Ethylene tetrafluoro-ethylene (ETFE)	Excellent	No change after > 100 cycles
Fluorinated ethylene propylene (FEP)	Excellent	No change after > 100 cycles
Polyacetals	Good	Colour change and loss of gloss. Slight to significant change may occur after > 100 cycles Contact equipment manufacturer
Polyacrylates (e.g. PMMA)	Good	Slight to significant material change may occur after 10–100 cycles Contact equipment manufacturer
Polyamides (e.g. Nylon)	Good	Colour change and loss of gloss. Significant material change after 10–100 cycles
Polycarbonate (PC)	Excellent	Slight surface change and loss of gloss. No significant change after > 100 cycles
Polyesters, saturated	Excellent	
Polyethylene (PE), various densities	Good	Colour change and loss of gloss. Significant material change may occur after 10–100 cycles
Polyimides (e.g. PEI)	Excellent	Slight surface change. No significant change after > 100 cycles
Polyketones (e.g. PEEK)	Excellent	Unfilled PEEK only – avoid sharp edges. Colour change and loss of gloss. No significant change after > 100 cycles
Polypropylene (PP) natural stabilised	Good	Colour change and loss of gloss. Significant material change may occur after 10–100 cycles Polypropylene may not be good for multiple reuse
Polystyrene	Poor	Significant material or surface change < 3 cycles
Polysulfones	Good	Slight surface change and loss of gloss. No significant change after > 100 cycles

(*Continued*)

Table 7.7 Continued

Thermoplastics	Compatibility	Number of cycles polymer may be compatible
Polyurethane (PU)	Not likely	Significant material or surface change < 3 cycles
Polyvinylchloride (PVC) rigid	Excellent	Colour change and loss of gloss. No significant change after > 100 cycles
Polyvinylchloride (PVC) plasticised	Good	Surface change may occur after 5–25 cycles
Thermosets		
Epoxies	Variable	Significant material change may occur after 10–100 cycles, check reliability and stability
Phenolics	Excellent	Loss of gloss. No significant change after > 100 cycles
Polyester, unsaturated	Excellent	
Polyurethanes	Not likely	Significant material or surface change < 3 cycles; not good
Adhesives		
Acrylic	Good	Application specific. Contact equipment manufacturer
Epoxy	Variable	Application specific. Contact equipment manufacturer
Fluoroepoxy	Good	Application specific. Contact equipment manufacturer
Silicone	Good	Application specific. Contact equipment manufacturer
Elastomer		
Natural rubber	Not likely	Significant material or surface change < 3 cycles
Butyl rubber	Not likely	
Ethylene propylene dienemonomer (EPDM)	Fair	Significant material or surface change with < 3 cycles
Silicone	Excellent	Slight material change after > 100 cycles
Styrenic block copolymers	Not likely	Significant material or surface change < 3 cycles
Polychloroprene	Poor	While in an ozone normal environment, it is OK, but under sterilisation significant material or surface change may occur with < 3 cycles
Urethane	Not likely	Significant material or surface change < 3 cycles

Sources: AAMI TIR 17[1] and reference 13.

period. Ozone and oxidising agents are generally applied only to small niche and minimal-sized devices. They are predominantly used in hospitals, but less so in industry. While ozone and H_2O_2 are both oxidising agents, their effects are different.

Ozone may sterilise some cellulosics better than H_2O_2, but H_2O_2 sterilises butyl rubber, urethanes and natural rubber better than ozone. Silicones may be sterilised better by ozone than H_2O_2. Ozone should have the capacity to diffuse and penetrate deeper than peroxide, but less so than EO, dry heat, steam or irradiation.

7.6.2 Adaption of ozone sterilisation to minimise effects on polymers

Under some conditions, a sterilisation technique such as ozone, which is thought to be compatible with a polymer, will not be suitable when tested. This incompatibility is often due to changes in process parameters, environment or due to the formulation or stability of the sterilant. Ozone sterilisation is compatible with a wide range of commonly used materials, including polymers such as PVC, Teflon®, silicone, PP, PE and acrylics. Ozone consists of O_2 with a loosely bonded third oxygen atom, which is available to oxidise other molecules. A very short half-life means that high concentrations and new ozone generation is required to inactivate microbes at 30–5°C. By reducing temperatures to below ambient, yet above freezing, less ozone is required for sterilisation because it is more stable at lower temperatures; however, lowering the temperature may increase exposure time. Reductions in ozone concentration and temperature will reduce its effect on polymers.

7.7 Radiation sterilisation

Radiation sterilisation has excellent penetration capabilities and is a relatively rapid process. Sterilisation is typically achieved with ionising isotopes (e.g. ^{60}Co) in high-voltage accelerators. It is effective for many single-use medical materials and devices, but not for reusables. Initial capital costs are high, so it is not often used in hospitals, but mainly in the manufacture of disposable devices. Radiation is an inherently fast process, requiring only one dose (e.g. 15–45 kGy), resulting in ease of application. Polymer compatibility is the major limitation of this method and must be ensured before application. Radiation can initiate deep molecular changes in polymers, which require shelf-life testing to demonstrate that no continued damage results. Multiple resterilisations by this technique are not commonly practised.

7.7.1 Effects of radiation sterilisation on polymers

Irradiation can cause changes in polymers that other methods will not, such as bonds scission, crosslinking or a combination of both. Radiation may cause odours, discolouration, embrittlement and degradation, or affect bond strengths, which may cause changes over the life of a polymer implantation. Polymers particularly sensitive to radiation include unstabilised PP, acetals, some Teflons® (e.g. PTFE, PFA, FEP), polyglycolic acid (PGA) and polylactide sutures, polymethylpentene, polyvinylidene fluoride, polymethyl metharylate (PMMA), some acrylic adhesives, butyl rubber, some cellulose esters, natural liquid crystal polymer and (via cross-linking) silicones.

The effects of radiation on polymers may be influenced by:

- chemical composition and formulation of the polymer,
- polymer morphology (crystallinity, MW and density),
- radiation dose and dose rate,
- temperature.

An understanding of radiation chemistry helps to assess why a particular plastic is affected in a certain way. When a plastic is exposed to gamma radiation (from ^{60}Co at energies of 1.17–1.33 MeV), molecular bonds are broken. The polymer either recombines into its original configuration or, if scission occurs, the MW is reduced and the polymer is weakened. Conversely, where cross-linking occurs, a large three-dimensional matrix is formed and the polymer is strengthened. The effects of radiation may also be influenced by the age and environment of the polymer. Higher bond energies result in molecules that are more stable under irradiation, and polymers with a benzene ring are generally very stable. Examples of radiation-stable plastics are listed in Table 7.8.

7.7.2 Polymer degradation by radiation

All plastics are affected by irradiation to some extent. Some effects are favourable or negligible, while others are not. Post-irradiation effects, attributed to trapped free radicals, the presence of peroxides and possibly trapped gases, explain why a PP component acceptable today will shatter in 2 years' time.

- PE is predominantly cross-linked; slight odours may result. HDPE is more resistant than LDPE.
- PP (unstabilised, natural) and polymethylpentene undergo both cross-linking and scission. Embrittlement, breakage and discolouration can occur at higher sterilising doses.

Table 7.8 Compatibilities of some polymers for irradiation

- ABS (excellent)
- Elastomers – silicones (peroxides and platinum cured), TPE (SEBS, TPO), natural (Isoprene), EPDM, urethane, nitrile, butyl, styrene-butadiene
- Fluoroplastics (other than PTFE an FEP) – PVDF, PCTFE, PETFE

PTFE and FEP may be adversely affected by irradiation

- 'High-end' engineering resins, PEK, PEEK, Polyetherimide
- Acetal is adversely affected by irradiation
- Nylons (polyamides), especially aromatics, 12,11, 6/12 and 6/10

Nylon may degrade oxidatively in applications that have large surface-to-mass ratios (e.g.films, fibres, adhesives)

- Polyethylene, LDPE < LLDPE, HDPE, UHMWPE

(high-density PE is more radiation-resistant than low-density PE)

- Polyesters (PE) and PETG
- Polycarbonate (PC) and alloys
- Polysulfone (PSF)
- Polyvinyl chloride (PVC) flexible and semi-rigid, colour, plasticiser and HCl corrected
- Polyurethane (8 chemical varieties). Aromatics may discolour some
- Polypropylenes (stabilised) and Copolymers (PPCO) and polymethyl pentene – radiation-stabilised are good

(natural polypropylene (unstabilised) has little tolerance to irradiation)

- Polystyrene and copolymers, ABS, PS, SAN
- Polyacrylics (PA, PMA, PAN)
- Thermosets – epoxies, phenolics, polyimides, polyurethanes, polyesters

Sources: AAMI TIR 17[1] and references 1, 3, 4 and 5.

- Polystyrene is very stable to radiation because of its benzene ring, although it may begin to yellow above 50 kGy.
- ABS is much less resistant to radiation than polystyrene, but it may be suitable for single-dose irradiation.
- PVC can discolour with irradiation, and it may produce HCl and leach plasticiser.
- Acetal or polyformaldehyde (POM) copolymers are sensitive to radiation and their chains are easily broken (embrittlement); the material often changes from solid to dust, colour from yellow to green.
- Polyamides (nylons) are sensitive to cross-linking, but many are suitable for a single dose; some multiple dose.

A polymer with high radical yields (e.g. G-values) after irradiation is less stable. Oxidation, caused by the presence of oxygen in the gamma-radiation process, can decrease cross-linking and increase degradation, or produce a tendency for chain scission to occur. Oxidation also causes peroxide,

carbonyl and hydroxyl groups to be formed. Post-irradiation effects explain why PVC tubing may not be compatible with certain drugs.

A few plastics are adversely affected by radiation doses of 25–40 kGy; others can be sterilised at lower doses (11–30 kGy). Many polymers are compatible with sterilisation doses of about 25–40 kGy; however, they deteriorate at higher doses or after multiple sterilisations (see TIR 17[1]). PTFE and PFA degrade at low doses, POM above 25 kGy and butyl rubber at slightly higher doses, depending on the grade. Table 7.9 below shows compatibility variations for sterilisation between 25 and 40 kGy.

While the resistance and degradation of the above polymers may vary, other factors may determine their biocompatibility and compatibility with radiation sterilisation.

- Phenolic antioxidants contained in most polymers are responsible for discolouration.
- The elastic modulus of a polymer may be affected by more than one dose of radiation.
- Fillers and reinforcing materials improve the radiation stability of adhesives, coatings and potting compounds. Adhesives, films, fibres, coatings and encapsulates react much the same way to irradiation as the materials from which they are derived.
- Nucleation may increase embrittlement.
- Electronic boards and circuits are not always compatible.

ABS and polycarbonate are generally compatible with one dose of radiation, but may not be sterilised up to 100 Mrad. Both may discolour, with ABS discolouring the most. ABS/polycarbonate blends lose physical properties linearly with an increase in radiation dose. Acrylic polymers are sensitive to radiation as a result of scission of the ester chain. Polymethyl methacrylate (PMMA) has been used in dosimeters because it is sensitive to radiation doses. Radiation-compatible acrylics, however, are available, but not typically for implantable or ophthalmic devices; optical clarity of PMMA may be affected.

7.7.3 Adaption of radiation sterilisation to minimise effects on polymers

With irradiation, there are frequently trade-offs to be considered to minimise effects on polymer properties. The effects of radiation on a polymer may be modified by:

- changing its chemical composition and formulation,
- modifying its morphology (crystallinity, MW and density).

Table 7.9 Compatibility variations for sterilisation between 25 kGy and 40 kGy

Polymer type	Resistant types	Evaluate or check	Degradation
Thermosets	PUR, phenolics, etc. polyimides, epoxies	Polyurethane	
Polyolefins	PP, PE, HDPE	PP, HDPE	Unstabilised or natural PPHDPE not as stable as low molecular weight
Technical thermoplastics	EVA, EVOH, ABS, ABS/PC, PA 6, PA 66, PET, PBT, PVC, Acrylics	PMMA, PC, PVC	POM (Acetal); aliphatic nylon degrades oxidatively when used in applications that have large surface-to-mass ratios (e.g. films, fibres, adhesives) PMMA too affected and discoloured for some applications (e.g. contact lenses)
Fluorocarbons	Perchlorotrifluoroethylene (PCTFE), polyvinylidene fluoride (PVDF), ethylenetetrafluoroethylene (ETFE)	Fluorinated ethylene propylene (FEP)	Perfluoroalkoxies (PFA), polytetrafluoroethylene (PTFE)
High-performance thermoplastics	UHMWPE, PA 46, PA 11, PA 12, PPA, PAA, PPS, PPO, PSU, PPSU, PI, PAI, PEI, PEEK	UHMWPE	Oxidation embrittles UHMWPE, and will continue to occur during *in vivo* use
Thermoplastic elastomers (TPE)	SBS, SEBS	PP/EPDM, PEBA, TPU, COPE (ether–ester copolymer)	
Elastomers	NR, NBR, HNBR, SBR, silicone	Chlorobutyl rubber, neoprene, EPDM, EPR	Butyl silicones can cross-link and become too stiff for some applications (e.g. prostheses)
High-performance elastomers	Fluoroelastomers, fluorosilicones	Silicones, AEM/ACM	Silicone can cross-link
Liquid crystal polymer (LCP)	Commercial, natural	Commercial LCP	Natural LCPs are not stable

Source: AAMITIR 17.[1]

Note: Polymers listed under the column 'Degradation' may be applicable with caution under certain unique situations, formulation changes, nitrogen inert gas, or low dosage.

If PP is modified with additives and stabilisers, it may become more resistant to irradiation. However, conventionally stabilised PPs may not be suitable for sterilisation by high-energy radiation doses (e.g. >30 kGy) because of the severe embrittlement and discolouration that occur immediately in the plastic. There are, however, several alternatives in the design of propylene polymers and formulations that solve these problems and yield resins suitable for irradiation at dosages up to 50 kGy. Early radiation-tolerant PPs were homopolymers stabilised with small quantities of phenolic antioxidants and large amounts of sulphide diester secondary antioxidants; however, these additives can discolour slightly after irradiation, depending upon the dose applied.

Modern resins that can withstand irradiation exhibit reduced crystallinity, narrow MW distribution and are formulated with hindered-amine light stabilisers, thus containing no discolouring phenolic antioxidants. Ethylene-containing random copolymers are also useful substrates for building radiation-tolerant formulations, as are homopolymers with low isotacticity or to which hydrocarbon oils or greases have been added. The hindered amines are, by themselves, non-colouring in PP, but they can interact with phenolic antioxidants to produce extremely deep yellow colours after irradiation. Therefore, when hindered amines are used in a PP formulation, phenolic antioxidants must be not be used.

Reducing the irradiation dose (e.g. from 25 to 15 kGy) also results in enhanced stability of polymer properties. The use of nitrogen in place of air helps to reduce the effect of oxidation of some polymers. Reducing the temperature down to 10°C or lower (e.g. dry ice), or even that of liquid nitrogen depending upon the material, also allows sterilisation of very sensitive biomaterials.

The use of antioxidants in irradiated polymers is important. For example, vitamin E improves the oxidative resistance of irradiated PE, but the mechanism of action is unknown. The use of other antioxidants may have synergistic effects on the wear and mechanical properties of irradiated PE. The application of electron beams instead of gamma irradiation also enhances the properties of a number of polymers, because of the speed of irradiation and lack of oxidation/ozone effects produced from gamma irradiation. This may be also true with X-rays. X-rays will result in less temperature generation compared with the impact of electrons on materials.

Aromatic materials are more resistant than aliphatic materials (e.g. PU); aliphatic PU may break down to relative toxic compounds (e.g. 4,4′-methylenebisphenyldiamine or methylenedianiline (MDA)).

- The use of non-phenolic additives will usually eliminate discolouration problems caused by phenolic antioxidants.
- Although natural PP and polytetrafluoroethylene (PTFE, Teflon®) are typically unstable when irradiated, alternatives and solutions are available that make radiation more suitable.

- PVC and PP should contain heat stabilisers to improve radiation compatibility.
- High levels of antioxidants improve radiation stability, so, in general, levels should be increased if the product is to be radiation sterilised.
- Within a given polymer class, the lower the density the greater the radiation stability.
- If copolymerisation of a sensitive material is possible, it should be attempted.

Some electronic boards or circuits are compatible with low irradiation doses. Premature ageing of plastics may occur due to the oxidative effects of irradiation; consequently, it is always prudent to evaluate accelerated ageing of plastics to assure that this is not a problem under real-life conditions. Some Teflons®, despite their high heat resistance, are degraded by radiation, although some thin films/coatings and certain types of Teflons® have been shown to be radiation-compatible at low doses.

- PE, which is predominantly cross-linked, is compatible with radiation by sterilising in nitrogen rather than in air (with oxygen). Slight odours can be reduced through modification of the formulation.
- Breakage of PP syringe tips has been used for blood-borne disease procedures in disposure of needles, with the needles on end of the tips.
- Radiation-stabilised propylene polymers are available, using high MWs, copolymerisation and alloying with PE containing additional stabilisers. Use of electron beams at high irradiation dose rates may further reduce the oxidative degradation of PP.
- Polymethylpentene is similar to PP, but can be irradiated at low doses.
- High-impact grades of ABS are less radiation-resistant than standard grades.
- PVC can be compatible with radiation, but release of HCl, discolouration and plasticiser leaching must be prevented. Addition of antioxidants and heat stabilisers helps, as does changing the plasticiser (DEHP or DOP) to one that is less toxic and non-carcinogenic.
- Resterilisation using radiation is not normal, although plasticised PVC may be resterilised.
- Among the polyamides (nylons), nylon 10, 11, 12 and 6–6 are more stable than nylon 6. Nylon films and fibres are less resistant to radiation.

Some general considerations when selecting plastics for irradiation:

- Use aromatic polymers (e.g. benzene rings are more stable than aliphatic polymers).

- Material degradation may be reduced by effective device design and material selection – that is, the use of materials with appropriate additives and modifications in the polymer chains.
- Although electronic components are typically not compatible, an increasing number is compatible with irradiation.
- Another means of overcoming compatibility issues in some cases is through the reduction of sterilisation dose required to achieve the desired sterility level. Also, it is important to note that the compatibility of materials is a strong function of the application, and the related material stresses. For example, in some cases it is possible to utilise Teflon® with radiation sterilisation despite it not being generally acceptable.

Additional information about radiation sterilisation material compatibility is provided in AAMI TIR 17.[1] Biocompatibility and functionality need to be evaluated depending on the end use of the polymer and conditions under which it will be used. Radiation is increasingly used for sterilisation of many polymers in numerous medical devices by means of additives and modifications to the polymer chain.

7.8 Sterilisation and polymer efficiency

The aim of sterilisation is to destroy all microorganisms on the surface of an article, in a fluid or within a polymeric product for implant, to prevent disease transmission associated with the use of that item. The concept of what constitutes 'sterile' is typically measured as a probability of sterility for each item to be sterilised. This probability is commonly referred to as the sterility assurance level (SAL) of the product and is defined as the probability of a single viable microorganism occurring on a product after sterilisation. SAL is normally expressed a 10^{-n}. For example, if the probability of a spore surviving were one in one million, the SAL would be 10^{-6}. In short, SAL is an estimate of lethality of the entire sterilisation process and is a conservative calculation. SALs for implantables are 10^{-6} and the choice of a 10^{-6} SAL was originally strictly arbitrary and is not been linked with any adverse outcomes, except possibly when measured incorrectly (e.g. from a surface of a product and not within a product for implantable).

The possibilities for polymers to be implanted in the human body are vast. Polymers used for implantation must be sterile, safe and non-toxic after sterilisation. Manufacturers or healthcare facilities must ensure that products to be implanted are entirely sterile after sterilisation. The types of polymers that can be implanted without harmful effects reflect the efficiency of different sterilisation techniques.

There are always trade-offs when selecting a method of sterilisation. Depending on the inherent properties required for medical devices and

products, a sterilisation technique must be selected that is compatible with the polymer materials to be used. As the use of polymers in medical devices and implants increases, it is important to understand the purpose of sterilisation, as well as the effects of different techniques. This includes not only sterility but also biocompatibility and physical/chemical compatibility.

7.8.1 Sterility entirety

Sterilised polymer implants must be entirely sterile, both within the polymer and on its surface. It is vital that polymers and biomaterials to be used as implants are sterilised in their entirety. Microbes (spores) trapped within polymers will typically be more resistant to sterilisation than those on the surface, and over time may activate, germinate and grow out from their trap site, thus infecting the human host.

The sterility of a product must be totally evaluated, not just on surfaces but also in areas within polymers. Thus, only sterilants that are capable of penetration should be used. Hydrogen peroxide, steam and ozone are not penetrable sterilants unless materials are highly porous. In contrast, dry heat, EO and irradiation are permeable to many materials. Electron beams are less penetrable than gamma or X-ray irradiation, and steam is less penetrable than dry heat for many polymers. PE is not permeable to steam or humidity, but EO will drive humidity and moisture through LDPE films. Nylon is permeable to moisture, but not to EO; however, pre-humidification will enable EO to penetrate nylon films.

Sterility throughout the implantable material is essential when polymers are hydrophilic, biodegradable or degraded with time, such as wear degradation, for example, of ultra-high molecular weight polyethylene for load-bearing devices. Encapsulated or hidden bacteria in the material may be released after a period of time. All implantable products and polymers must be sterilised within packaging, which must be appropriate for the sterilisation used.

Handling packages that are still warm and/or wet may compromise the barrier properties of the sterile wrapper, and the potential for contamination is increased. Sterile packages should be thoroughly cooled and dried before handling. At the end of a drying cycle, packages may still be warm and moisture may be trapped inside. If warm packages are handled with unsterile hands or placed on cold surfaces where condensation may form, the sterility of the package may be compromised. If the sterility of a wrapped item is in doubt, it should not be used.

A sterilised implant must be quarantined until the biological test or dosimeter reading. If the implant is placed in the patient before the results of the biological test are received, and if the test subsequently indicates the sterilisation failed, the only treatment for the patient is antibiotics and/or possible removal of the contaminated implant. In a situation in which the

patient is anaesthetised, it may not be reasonable or safe to wait for the results of the biological test.

7.9 Comparative efficiencies of sterilisation techniques for different polymers

In the design and development of implantable devices requiring sterilisation, consideration should be given to the choice of polymers and the needs of the patient, including the performance requirements of the finished device. The final product must meet safety and efficacy requirements while providing benefit to the patient. Product requirements can limit the choice of polymers available for construction and ultimately determine the acceptable mode of sterilisation based on compatibility. Product design characteristics also influence the sterilisation technique selected.

Selection of polymers for biomaterials requires consideration of design, processing and performance, including biocompatibility, functionality and sterilisation. The effect of sterilisation on polymers is a key factor in device design. Polymers must be selected so that the final products are compatible with the sterilising technique. Optimal selection of polymers for implantation depends on the effect of sterilisation and any biological effects, which may be similar to hydrolysis or oxidation. Selecting polymers with an 'excellent' response to sterilisation and passing preclinical biocompatibility tests are both critical for implantation.

The following list indicates the response to different sterilisation techniques[1–3] of polymers and their applications.

Polymers

PE: radiation (good to excellent, but may give off gas; low and moderate density more resistant and can be resterilised; HDPE can undergo oxidation); EO (excellent); steam (poor to good, high density more resistant); dry heat (poor to fair, but lower temperature improves for high density); H_2O_2 (excellent); ozone (excellent).

Applications: orthopaedics, joint replacements, tubing, medical packaging.

PP: radiation (poor to good, stabilised, but single use only); EO (good to excellent); steam (good and excellent with heat-stabilised grades; can be resterilised); dry heat (good excellent at low temperatures (up to 135°C) with heat-stabilised grades); H_2O_2 (excellent): ozone (excellent).

Applications: catheters, sutures, syringes, surgical filaments, surgical meshes used to reinforce soft tissue where weakness exists (for example, in the repair of hernias and chest wall defects), medical packaging.

Polymethylpentene: radiation (fair to good); EO (excellent); steam (good/excellent): dry heat (good/excellent up to 170°C); H_2O_2 (unknown); ozone (unknown).

Applications: containers, covers for medical instruments, TPX film.

Copolymers (e.g. PE/PP, polyallomer): radiation (poor to good, stabilised, but single use only); EO (excellent); steam (good, excellent with heat-stabilised grades which can be resterilised); dry heat (good, excellent at low temperatures (up to 135°C) with heat-stabilised grades); H_2O_2 (excellent); ozone (excellent).

Applications: parenteral solution containers, packaging, instruments, pneumatic and lubricant lines, tubes.

Polystyrene: radiation (excellent); EO (poor to good, but millions of parts have been acceptably sterilised and some formulations can be resterilised 2–5 times); steam (poor to excellent, with syndiotactic styrene); dry heat (poor to excellent, with syndiotactic styrene); H_2O_2 (excellent); ozone (fair).

Applications: containers, parts in IV sets, petri dishes, sputum cups.

Styrene–acrylonitrile copolymers: radiation (good to excellent); EO (poor to good, but many parts acceptable); steam (poor to fair); dry heat (poor to fair); H_2O_2 (excellent); ozone (unknown).

Applications: dialysis devices, IV connectors.

PMMA: radiation (fair to good); EO (good); steam (poor to fair at low temperatures, but not re-sterilised); dry heat (poor to fair at low temperatures); H_2O_2 (fair); ozone (good).

Applications: bone cement, contact lenses, corneal prosthesis, grout for artificial joints, orthopaedics, ophthalmology lenses, in membrane oxygenators.

Polyvinyl acetate: radiation (good); EO (poor); steam (poor to fair); dry heat (poor to fair); H_2O_2 (excellent); ozone (unknown).

Applications: film.

PVC: radiation (good); EO (excellent); steam (poor to fair up to 120°C if no load); dry heat (poor to fair up to 120°C if no load); H_2O_2 (excellent); ozone (good).

Applications: blood bags, catheters, containers, endotracheal tubes, films, hearing aid components, IV tubing, drip chambers and packaging, shrink tubing, storage bags, in ventilation systems.

Vinyl chloride copolymers: radiation (good); EO (excellent); steam (poor to good (without load) up to 120°C); dry heat (poor to good up to 120°C); H_2O_2 (unknown); ozone (unknown).

Applications: films, packaging.

Polyvinylidene chloride: radiation (good); EO (excellent); steam (poor to fair up to 120°C); dry heat (poor to fair up to 120°C); H_2O_2 (unknown); ozone (Application: medical packaging. unknown).

Fluorinated polymers (polytetrafluoroethylene (PTFE), PFA, PCTFE, PVDF, ETFE, FEP): radiation (mixed, some poor (e.g. PFE, FEP and PTFE)); EO (excellent); steam (fair to excellent); dry heat (fair to excellent, up to 170°C); H_2O_2 (excellent); ozone (excellent).

Applications: artificial joints and vasculature, fibre optics, surface treatments, stopcocks, tubing.

Polyamides (nylons): radiation (poor to good, depending whether aromatic or aliphatic); EO (excellent); steam (poor to excellent); dry heat (poor to excellent); H_2O_2 (good, but one use only); ozone (good).

Applications: bags, catheters, films, kidney dialysis, laparoscopy devices, special packaging, nylon spike.

Polyesters: radiation (fair to good); EO (excellent); steam (poor to excellent); dry heat (poor to fair); H_2O_2 (excellent); ozone (excellent).

Applications: covers, films, IV infusion fluid containers.

Polysulfone (PSF)**, polyphenylsulfone**: radiation (excellent); EO (excellent); steam (excellent, can be autoclaved thousands of times); dry heat (good to excellent); H_2O_2 (excellent); ozone (good).

Applications: handles for dental instruments, ophthalmic scopes and lenses, endoscopic devices, dialysers.

Polyethylene terephthalate copolymers (PETG): radiation (good to excellent); EO (excellent); steam and dry heat (good to excellent up to 134°C); H_2O_2 (unknown); ozone (unknown).

Application: packaging.

Polyethylene terephthalate (PET): radiation (good to excellent); EO (excellent); steam and dry heat (good to excellent); H_2O_2 (unknown); ozone (unknown).

Applications: angioplasty balloons, woven vascular prostheses, vascular grafts of large diameters.

Cellulosics (cellulose esters, cellulose acetate propionate, Cellulose acetate butyrate, cellulose (paper, cardboard)): radiation (fair to good, esters degrade less than other cellulosics); EO (excellent); steam (poor to good at low temperatures, depending upon the cycle); dry heat (poor to good, but at higher temperatures, there may be charring char); H_2O_2 (poor); ozone (poor to good).

Applications: films, filters, haemodialysers, membranes, IV burette champers, packaging.

Epoxies: radiation (excellent); EO (good to excellent); steam (fair to excellent); dry heat (fair to excellent); H_2O_2 (excellent); ozone (fair to excellent).

Phenolics: radiation (excellent); EO (good); steam (fair to good); dry heat (fair to good); H_2O_2 (good); ozone (excellent).

Polyimides: radiation (excellent); EO (excellent); steam (excellent); dry heat (good to excellent); H_2O_2 (excellent); ozone (unknown).

PUs: radiation (good to excellent, better if aromatic); EO (poor to good; steam (poor to fair); dry heat (poor to fair/good, at low temperature); H_2O_2 (good); ozone (poor).

Applications: blood pumps, catheters, connectors, containers, enteral feeding tubes, lipid-resistant stopcocks, needleless syringes, vials, balloons, pacemaker leads.

Acetals: radiation (poor); EO (excellent); steam (fair to good, up to 120°C); dry heat (good to excellent, up to 120°C); H_2O_2 (excellent); ozone (good).

Applications: structural keels for prosthetic devices, stopcocks.

Polycarbonate: radiation (good to excellent); EO (excellent); steam (fair to good); dry heat (fair to excellent, up to 134°C); H_2O_2 (excellent); ozone (excellent).

Applications: blood sets, cases, covers, cardiotomy trocars, in drug delivery devices, IV connectors, reservoirs, surgical instruments, safety syringes, valve occludes.

ABS copolymers: radiation (good); EO (excellent); steam (poor to fair); dry heat (poor to fair); H_2O_2 (excellent); ozone (fair).

Applications: in IV sets: Luer syringes, roller clamps, spikes, Y connectors, in dialysis units.

Elastomers (rubber)

Butyl: radiation (poor); EO (excellent); steam (fair to excellent); dry heat (poor to good); H_2O_2 (good, but only one cycle); ozone (poor).

Applications: tubing, closures (but not implantables).

Ethylene propylene diene monomer (EPDM): radiation (good to excellent); EO (excellent); steam (good to excellent); dry heat (fair to good); H_2O_2 (fair to good); ozone (fair).

Applications: tubing, other uses (but not implantables).

Polyketones, polyether ether ketone (PEEK), polyaryletherketone: radiation (excellent); EO (excellent); steam (excellent); dry heat (excellent); (excellent); ozone (excellent).

Applications: cardiovascular, orthopaedic, dental implants and tubing.

Nitrile: radiation (good to excellent); EO (excellent); steam (fair to good); dry heat (poor to fair); H_2O_2 (fair); ozone (unknown).

Applications: surgical gloves.

Polyacrylic: radiation (fair to good); EO (fair, but only one cycle); steam (poor); dry heat (poor); H_2O_2 (fair); ozone (good).

Polychlorophrene: radiation (good); EO (good); steam (fair to good); dry heat (poor to fair); H_2O_2 (excellent); ozone (poor).

Applications: tubing.

Silicone: radiation (fair to good); EO (excellent); steam (fair to excellent); dry heat (fair to excellent, up to 200°C); H_2O_2 (excellent, but surface sterilant); ozone (excellent, but surface sterilant).

Applications: catheters, membranes, prostheses (prosthetics), tubing.

Sterilisation that is physically/chemically compatible with a polymer may not be biocompatible. Information in the above list for a specific polymer is not an indication that the polymer is biocompatible. Biodegradation and failure may occur with some polymers. It is the responsibility of the 'user' to determine the

suitability and biocompatibility of a polymer for its specific application. The presence of additives, plasticisers and stabilisers can significantly affect the stability of many polymers, including their suitability for a specific sterilisation. A material that is thought to be compatible with a technique will not be compatible if evaluated under other conditions (e.g. irradiation of HDPE under air will be different when processed under nitrogen). This incompatibility is often due to oxidation, stability, formulation and/or processing changes in the polymer.

7.10 Post-implantation effects

Post-implantation effects often result from changes to physical and chemical characteristics that manifest as slowly visible changes to polymers. Impurities may leach out to affect cells or tissue after polymers have been implanted. In a mixture of polymers, leaching from one might affect the other. The breakdown of a polymer (to monomer) can result from a variety of physical, chemical and biological forces. All polymers are sensitive to degradation, but to differing degrees.

Polymer degradation may result from one or more of the following:[6]

- heat,
- oxidation,
- mechanical energy,
- electromagnetic radiation (UV, gamma or X-rays),
- plasma,
- ultrasound,
- hydrolysis, including enzymatic-catalysed,
- bacterial contamination.

The first six conditions involve absorption of energy that breaks primary covalent bonds, forming free radicals which may continue to take part in secondary reactions. Free-radical depolymerisation may occur in carbon–carbon polymer backbones. Hydrolytic mechanisms occur with polymers with different atoms, with depolymerisation occurring via the reverse of polycondensation. Hydrolytic degradation occurs in polymers with unstable bonds, such as ester and amide bonds, both of which exist in PU.

Biological degradation may involve biological enzymes, bacteria, cellular tissue and organ effects, and either chemical or enzymatic hydrolysis. While physical and chemical polymer degradation is well known among engineers, biology has added biodegradation, the result of enzymatic, foreign body effects and hydrolytic and ionic 'rate' mechanisms on polymers.

Enzyme-catalysed hydrolysis may be highly specific. For example, primary chains of collagen or gelatin are cleaved at the N peptide bond on the lysine side, but a poly-lysine chain is not degraded. Enzymatic degradation

is typical in breakdown and restructuring of natural polymers, such as proteins in healing wounds and restructuring of tissues. It is also common in cellulosics, such as the breakdown of starches and sugars. While enzymes may influence polymer degradation, bacterial effects on an implanted polymer may be more significant. Bacterial infection will release other enzymes and acids, both involved in the hydrolysis mechanism of degradation.

Many polymeric medical devices and biomaterials, such as cardiovascular and orthopaedic devices, may appear to be initially passive in their tissue interactions. However, when heparised or with applied additives, polymers implanted for a prolonged time or permanently may not remain passive. The properties of polymers vary depending on their predisposition to physical and chemical degradation, exposure to bacterial infections and the site of contact or implantation.

Polymers will contact tissue and/or bone in devices such as orthopaedic pins and plates, pacemakers, breast implants, replacement tendons, ligation clips and drug supply devices. Implanted devices that contact blood, include pacemaker electrodes, heart valves, vascular grafts, ventricular assist devices, internal drug delivery devices and stents. The properties of implants will also vary with the length of time they are implanted in a patient. Typical times are:

- limited implantation (≤ 24 h),
- prolonged implantation (> 24 h, ≤ 30 days),
- permanent implantation (> 30 days).

One post-implantation effect of prolonged or permanent polymer implantation can be proliferation of blood vessels and connective tissue at the implant site caused by changes in chemical and physical properties and/or motion of the device.

Granulation tissue can occur as a result of healing inflammation. Its earliest appearance is three to five days post-implantation, cauterised by proliferation of fibroblasts and vascular endothelial cells. Neovascularisation, often observed as pink, soft granular structure on the surface of healing wounds, may consist of fibroblasts, proteoglycans (early), collagen (later, type I) and vascular endothelial cells. Fibroblasts resemble smooth muscle cells and are responsible for wound contraction.

A 'foreign body reaction' is considered part of the normal wound-healing response to implanted biomaterials (polymers), which may persist for the lifetime of the implant. It consists of granulation tissue components, such as macrophages, fibroblasts, capillary formation, foreign body giant cells and fused macrophages, and may be involved in biodegradation of polymeric medical devices.

Fibrosis/fibrous encapsulation may also occur post-implantation. This is an end-stage healing response, which isolates implant and foreign body reaction from surrounding tissue. There are local and systemic factors where cells may grow or differentiate following injury, such as atrophy, hypertrophy, hyperplasia and metaplasia, as well as the production of different or too many proteins.

Biomaterial selection depends on the end use. Compatibility in one application does not ensure compatibility for another. Polymer and device characteristics to consider include chemical, toxicological, physical, electrical, morphological and mechanical properties, the effect of sterilisation, the conditions of tissue exposure and the nature of any risks.

It is essential to avoid potential toxicity problems arising from the sterilisation process in the case of medical devices that come into contact with human tissue (e.g. catheters, surgical tools and containers used for transplant preparation and storage). Because it may not be possible to predict the effects of every combination of material and sterilisation process, a simple test can be performed to ensure the absence of cytotoxicity. The test involves culturing a non-adherent cell line in direct contact with the test material, in micro-wells attached to the surface of the test device. Using this approach, sterilisation may be compared for each material considered for implantation.

Implantable polymers must:

- have good handling characteristics,
- be compatible with infection,
- be strong enough to prevent failure,
- invoke favourable host response (biocompatible),
- not limit post-implant function,
- not restrict future access,
- not shrink or degrade over time,
- be easy to manufacture,
- be inexpensive,
- not transmit infectious diseases,
- be sterilisable.

Degradation properties of polymers depend on the type of polymer used, its specific biological application and sterilisation technique employed.

7.11 Dry heat sterilisation of silicones

Reasons why dry heat is the best technique for silicones are outlined. Silicones are used for breast implants and other prosthetics because they do not absorb surrounding liquids and remain stable over a long period

after implantation. Successful sterilisation of breast implants using EO depends on the quantity of viable bioburden and presence of non-viable materials, including oils, proteinaceous films and extraneous production debris. Accumulation of oils and hydrophobic substances can agglomerate microbes, protecting them from the EO sterilant. Breast implants filled with silicone gel and oils are particularly inappropriate substances for this method. In addition, EO is highly absorbed by silicone gels, requiring extremely long times for off-gassing of EO residuals, which may not be reduced to safe limits.

Breast implants and other silicone prosthesis often have multiple cavities and imperfections, which can harbour bioburden. Steam sterilisation is not a viable alternative to EO for these multiple impenetrable cavities with non-hydroscopic surfaces. Irradiation could be an alternative, but it causes cross-linking of the polymer that causes stiffness. Gross microbial contamination of silicone prosthesis and multi-lumen implants could result from the application of steam or EO sterilisation, with viable microbes constituting a significant risk of infection with prolonged implantation.

Most silicone implants cause no macrophage or other tissue reaction, except for the effect of capsule formation to provide a sheath. In a minority of patients, however, foreign body reactions occur, possibly due to silicone fragments from a fragmented implant. Silicones may induce tumours (e.g. sarcomas) subcutaneously, but this is not due to the sterilisation technique. Pulverised silicones create no tumours and thus are not chemically carcinogenic. However, solid silicone may induce tumours after implantation. Silicone gels used in breast implants have caused problems from bacterial infections of tissues and circulatory systems.

Most implants undergo one or more thermal treatment during their production, coincidental with extrusion, moulding, vulcanisation, etc., which should impart some sterilisation or decontamination of heated components. Applying good clean room conditions, subsequent dry-heat sterilisation is expected to impart sterility to silicone implants and prosthesis. Silicone is highly heat resistant. Dry-heat sterilisation is well established for silicone implants, provided bioburden quantities are kept low and under control. It is sufficiently developed and validated to yield reliable silicone products with an excellent level of sterility assurance. For practical purposes, sterilisation never leads to an absolute sterile product, unless performed at temperatures that carbonise the organic matter of which microbes are composed. Silicone is not an organic material, and thus can withstand extremely high temperatures.

After implantation, elevated enzymatic activity can be observed, but enzymes have little effect on silicones. Certain silicone rubber heart valves may absorb some lipoidal content from blood, which in turn may lead to cracks in the heart valve.

7.12 Ethylene oxide (EO) sterilisation of polymers

7.12.1 Polypropylene – steam or EO sterilisation

Polypropylene is less toxic and more biocompatible with tissues than PE. However, to be compatible with irradiation, natural PP must be modified by incorporating additives (or by copolymerisation) capable of scavenging free radicals and preventing further oxidation. Subsequently, it is less biocompatible than natural PP. Techniques other than irradiation are thus preferred for natural PP to ensure biocompatibility. PP is more susceptible to strong oxidising agents (e.g. ozone) than PE. Heat-stabilised PP for orthopaedic implants can be sterilised using steam.

PP has been used in small sections for various surgical needs. Hydrolytic enzyme effects on PP are minimal, but it may degrade due to oxidation. However, the amount needed to construct a breast implant turns out to cause significant problems for patients. PP is a spongy material that may absorb liquid and expand after implantation. The risk of rapid expansion poses serious problems, and consequently PP is not recommended for breast implants.

PP surgical mesh can be sterilised using steam or EO. Complications that may occur following implantation of any surgical mesh include infection, inflammation, fistula formation, extrusion and adhesion formation when placed in direct contact with the intestine. Any implanted material must not be physically modified by tissue fluids, be chemically inert, not incite an inflammatory or foreign body cell response, be non-carcinogenic, not produce allergic reactions, stand up to mechanical stress and be capable of low-cost fabrication and sterilisation without tissue reaction.

PP, which is frequently used as an implantable mesh, induces remarkable chemotactic activity in tissues adjacent to a hernia prosthesis. PP may stimulate the immuno-competent cells of patients with prosthetic implants. The extent of foreign-body reactions is also influenced by PP filament structure and surface area, both of which favour monofilament materials. Tissue response to lightweight PP is characterised by a lower chronic inflammatory response than heavyweight PP. PP has been used as non-biodegradable sutures in eye operations and also in heart-valve structures.

In many situations, steam sterilisation temperatures may be too high to allow polymers and biomaterials tolerant to only low temperatures to function properly after sterilisation. Whereas heat-stabilised PP is more compatible with steam sterilisation, unstabilised PP may be degraded by heat. Degradation of PP may occur after three autoclavings. Consequently, EO is the preferred sterilisation method if more than one resterilisation is needed. If not, then steam sterilisation of a PP mesh should be carried out only once.

7.12.2 Acrylics – EO sterilisation

Acrylics are available as rigid, heat-cured, preformed materials of high clarity, widely used in intra-ocular lenses, or as cold-curing 'dough' that can be moulded and shaped into any form. The latter form is widely used in bone cements for orthopaedic applications. Acrylics have been used as implantable ocular lenses, bone cement for fixation of joint prosthetics or dentures, and maxillofacial prostheses.

Perspex gamma radiation is an acrylic that must be sterilised with dry EO as wet (> 0.5% relative humidity (RH)) EO may cause crazing. However, typical and impact-modified acrylics are compatible with EO sterilisation cycles with %RH.

PMMA is used in orthopaedic surgery to fix prosthetic components. Two additional post-sterilisation uses, which rely on its moulding properties, are in dentistry. PMMA is also used as a bone graft template and as a femoral window plug in total hip replacement. The use of PMMA bone cements to fix artificial prosthesis to the human body has become common in orthopaedic surgery. Hip and knee joints have very complex biomechanics and support high loads. Hence, acrylic bone cements must comply with international standards to ensure the bio-functionality and durability of the implant.

Acrylics are borderline sensitive to irradiation, and would not last long if used for implantation. While no new chemical entity is produced in the plastic after irradiation, irradiated lenses have produced tissue responses in patients. EO is a gentler sterilant than irradiation and improves the possibilities of implantation. A heat-resistant form of PMMA would be useful. During the manufacture/processing of PMMA, the polymer should not exceed 140°C to avoid liberation of monomer. After implantation the latter could escape into surrounding tissue and cause prolonged irritation.

The problems of contact lens-induced chronic inflammation (e.g. contact lens-induced papillary conjunctivitis) and acute inflammation (e.g. acute red eye) are less well-understood. Protein deposits, lens ageing, occlusion, mechanical effects and bacterial contamination have all been implicated. There is a need to understand and avoid what stimulates low-grade irritation and inflammation by making contact lenses more comfortable and improving their compatibility with the ocular surfaces.

For other implantation sites, cure-in-place PMMA formulations are used successfully. However, in PMMA bone cements, fibrous tissue capsules may occur that give rise to a foreign body reaction. The use of acrylics in dentistry can also lead to irritation and inflammation, especially, if toxic monomers occur as a result of excess heat in polymer manufacture.

7.12.3 Polyethylene – hydrogen peroxide or EO sterilisation

Ultra-high molecular weight polyethylene (UHMWPE) is used in orthopaedic implants, particularly at surfaces subject to high stress, such as those in hip or knee replacements. However, PE of lower MW could not withstand such stress. Radiation sterilisation is feasible for high MWs, but EO is preferable at low MWs. Aeration is required to remove toxic EO residues to avoid irritation of tissues, carcinogenicity, haemolysis, etc. The higher the MW, the more difficult it is to produce a homogeneous melt, and greater the risk of degradation before sterilisation. Degradation of PE is uncommon, except with irradiation.

Oxidation of UHMWPE by gamma irradiation results in some degradation. The extensive oxidation of UHMWPE after gamma irradiation or thermal treatments (e.g. steam or dry heat) can continue after implantation. EO is a viable alternative to gamma irradiation that avoids oxidation and fatigue-related degradation of load-bearing PE surfaces in total joint implants. PE tibia inserts have been used in a two-stage exchange arthroplasty of infected knees. Increased intensity or dose may require re-evaluation of sterilisation effects on PE implantation. Tissue necrosis does not typically occur with implanted PE, but there is considerable fibrosis.

Despite its excellent material compatibility with joint replacement materials, EO may not be suitable for sterilisation for other reasons. The cost of setting up sterilisation chambers, process monitoring and environmental management may not be justifiable. Hazardous materials training, protective attire and risk management, as well as EO recovery and regulatory paperwork, also add to operating costs.

Hydrogen peroxide (H_2O_2) appears to have the least problems associated with sterilisation of PE for implantation. There are no EO residues and processing with H_2O_2 is much faster, with sterilisation cycles less than three hours, including aeration. Vaporised hydrogen peroxide (VHP) provides for faster turnaround times than EO sterilisation, including reduced incubation for quick product release. Consequently, the VHP process is preferable for UHMWPE liners – for example, in hip replacements.

7.12.4 Polyurethane – steam, EO sterilisation or irradiation

Medical device applications of PUs include blood pumps, catheters, connectors, containers, enteral feeding tubes, lipid-resistant stopcocks, needles syringes and vials. Because of the possible complex behaviour of implantable PUs in the body, fabricators of PU-containing devices must pay particular

attention to the choice of composition and component design. Subsequent treatment during qualification, fabrication, sterilisation, storage implantation and *in vivo* operation may determine the performance and enable assessment of the efficacy of PU as an implant material.

PUs are a combination of ester and amide groups, which are vulnerable to hydrolytic decomposition. However, PU is also fabricated with an ether bridge, resulting in a polyether urethane (PEU). Steam and EO sterilisation may both cause MW reduction. Their use will depend upon the degree of MW reduction, which varies with hydrophilicity of the polyether segment. EO and irradiation sterilisation provide better results. The ester bond is more susceptible to degradation and cleavage if the PU is exposed to excessive heat in the presence of water (e.g. steam sterilisation). Hydrogen peroxide sterilisation is not used because PU is an absorber of the peroxide, which degrades the polymer. Dry-heat sterilisation may be compatible with some PU formulations at lower sterilising temperatures.

Isocyanates used in PU manufacture can induce allergic responses. Potential carcinogenic activity will vary significantly between different PU formulations. Steam or radiation sterilisation of some PU formulations may create toxic by-products – for example, 4,4′-methylenebisphenyldiamine or MDA.

Some PU sponges have caused tumours. However, PU is used as a material for prolonged or permanent implantation, as in pacemaker leads. Cardiac pacemakers frequently become infected and have to be removed. The same can occur with reused instruments. However, reuse should only be the cause of infection if cleaning and sterilisation procedures have failed to achieve sterility.

Use of PU may result in less firm encapsulation than occurs around silicone implants. However, PU implants cause less allergic reaction than silicone under some circumstances. PEU elastomers replaced silicone rubber for pacemaker lead insulation because they provide superior mechanical properties, are biocompatible (causing less allergic reaction) and were thought to be bio-stable. Although initial results were promising, over two decades of experience with PEUs have shown that these materials are not always bio-stable. In the case of PEU pacemaker leads, H_2O_2, a known product of inflammatory cells involved in the foreign-body response, permeated the outer insulation. The actual degradation of the PEU occurs when the H_2O_2 reaches the outer conduction coil of the lead where it decomposes into hydroxyl radicals, which subsequently cause chain scission in the soft ether segment, as observed *in vitro*. Localised regions of intense physical damage and chemical degradation occur in sections of the lead that are at least exposed initially to a high concentration of H_2O_2 from local cellular activity and large, repeated strains due to inter-corporeal movement. Chemical degradation and physical damage may have a synergistic effect on failure of the insulation.

7.13 Sterilisation issues relating to biodegradable polymers and coatings

Biodegradable polymers are useful for fabricating implantable medical devices, and as coatings for medical devices. Biodegradable polymers are biocompatible and may be tuned to provide optimum bioactive agent elution rates as well as degradation rates. Both medical devices and medical device coatings can use biodegradable polymers.

7.13.1 Biodegradable polymers

Commercially available biodegradable polymers are used in orthopaedic fixation devices, dental implants, ligature clips, sutures, tissue staples and skin-covering devices. Examples of the most widely used biodegradable polymers are polyhydroxyl acids, such as polylactic acid (PLA), PGA and their copolymer polylactic-*co*-glycolic acid (PLGA). Implants using these polymers are only required to last for weeks or months. The behaviour of these implants is determined by their glass transition temperature, which can be as low as 10°C. Residual stresses may remain in moulded parts after manufacture, leading to deformation on heating above the transition temperature.

PLA, PGA and PLGA are hydrolytically unstable. Hydrolytic degradation is influenced by water, moisture, steam, humidity, heat, acid, alkali and enzymes. Consequently, these polymers are affected by moisture during sterilisation. Steam or dry heat can lead to hydrolysis of the implants as well as deformation at higher temperatures. EO may cause some hydrolysis from the humidification step, and chemically may lead to moisturisation of the polymer. Additionally, EO sterilisation at 50–60°C and 40–50% RH is above critical temperature for these polymers. At 40–50% RH the activated surface of PGA absorbs water, which enhances degradation. For EO sterilisation to be effective it must be performed under very low % RH conditions. Complete removal of residual traces from the gas is also difficult to achieve. H_2O_2 is a surface sterilant, and the bioresorbable implant may need to be sterilised in its entirety to preclude patient infection during degradation. However, H_2O_2 is compatible with PGA, PLA and other sutures.

PGA and PLA typically do not survive irradiation. Irradiation at 25 kGy may induce degradation of the polymer chain, resulting in reduced MW and influencing mechanical properties. However, radiation sterilisation at lower temperature (e.g. 10°C, dry ice) may be effective at low doses (e.g. 16 kGy or higher). While immediately after irradiation at some doses, the tensile strength of PGA is insignificant, tensile loss may become significant after only seven days of implantation under a physiological environment.

When a polymeric material reaches the final stages of its degradation process, biodegradable material may cause a local foreign-body reaction.

In most cases, the symptoms of this tissue response are subclinical and pass unnoticed, but in some patients a clinical inflammation ensues. Reactions include a painful erythematous papule or a sinus discharging polymeric debris for up to six months. In severe cases, extensive osteolytic lesions may develop. For implants made of polyglycolide, the average incidence of such reactions may be 5%. However, when slow-degrading polymers are used, the incidence is lower. Tissue responses to polyglycolide manifest themselves, on average, around 11 weeks after surgery. Foreign-body reactions to devices made of poly-L-lactide can emerge as late as four to five years after implantation. A poorly shaped bone section, the use of a quinone dye as a polymer additive and an implant with a large surface area may lead to factors with increased risk of a foreign-body reaction. Laboratory experiments indicate that it may be possible to diminish the risk of an adverse tissue response by incorporating alkaline salts or antibodies to inflammatory mediators in the implants.

A biodegradable PU and a naturally derived polymer, gelatin, are used for liver manufacture. The structural design of some PEUs may allow both radiation and EO sterilisation. However, steam, irradiation and EO sterilisation will cause MW reduction. Biodegradation of PEU may be due to hydrolytic action on polyester and amide groups, or due to instability of the ether bond to oxidative deterioration.

Polyhydroxyalkanoates (PHAs) – for example, polyhydroxybutyrate [poly(3HB)] and poly-3-hydroxybutyrate-*co*-poly-3-hydroxyvalerate [poly(3HB-*co*-3HV)] containing 4–30 mol% hydroxyvalerate – are plastic-like polymers produced naturally by many types of bacteria. They are among the most promising future plastics because they are biodegradable and may be produced using renewable resources. PHAs are moisture-resistant polyesters and films can be sterilised by conventional methods (heat treatment and gamma irradiation), with no impact on strength.

Collagen, a natural biopolymer, is used as a biomaterial in surgical sutures and also used in solution to eliminate scar crypts serving as drug delivery vehicles. Sterilisation of collagen solution without deterioration is complicated because heat denatures it, but other methods are not typically applicable to solution. Sterilisation of cross-linked collagen fibres, films, membranes and sponges has been performed by irradiation and EO. Sterilisation by irradiation at doses greater than 50 kGy may lead to loss of crystallinity, increase in solubility, as well as other changes. Residues must be evaluated in the case of EO sterilisation because natural materials may lead to EO by-products.

Glutaraldehyde may be another sterilisation method, but its residues may elicit tissue toxicity after implantation. Also, it is difficult to maintain sterility after processing because of the need to remove residues without a package barrier. Tests should be performed to determine how much of the product or compound is absorbed by the body and to determine its effects over time.

7.13.2 Coatings

Coatings play an important role in implantable devices by improving the functionality the polymers used. Possibilities include: improved surface quality to enhance lubricity; improved resistance to friction, chips and impact for device protection; improved adhesion of tissues to polymer materials; special bio-functions, such as inhibition of blood coagulation via coatings with anti-clotting properties; hydroscopic or hydrophobic surfaces that help to absorb body constituents or drugs or resist absorption (e.g. of drugs) so that therapeutic activity can be maintained. The use of medical devices can be expanded by 'surface modifiers' that add a variety of important properties. For example, via coatings, enhanced biocompatibility can be achieved at low cost without changing the polymers from which a device is fabricated.

Consequently, selecting a sterilisation technique that is biocompatible and physico-chemically compatible with such coatings is important. For example, the use of hydrophilic polymers as a coating for medical devices is of particular interest. Steam or humidity in ethylene oxide and ozone sterilisation may cause these hydrophilic coatings to swell and become non-functional or unuseable. However, non-hydrophilic coatings are more compatible with humidity or steam. When used subsequently in implantable devices, they must, of course, be biocompatible after the selected sterilisation technique.

7.14 Biocompatibility testing[5]

An essential material safety requirement for polymers used in medical applications is biocompatibility. New implant designs and polymers must receive careful, preclinical evaluation. The materials and the processes used in device manufacture must be selected to ensure that the device is biologically safe for its intended use. The manufacturer must take into account the sterilisation process and the intended shelf-life of the device. Biological hazards include minor symptoms, such as irritations, to obviously serious toxicological symptoms, such as mutations and cancers, reproductive/developmental toxicants, as well as malfunctions.

The effects of polymers after implantation must be analysed, evaluated and studied by a series of biocompatibility tests prior to implantation. Subsections 7.14.1 to 7.14.12 refer to ISO 10993 standard and references 7 to 15.

7.14.1 Genotoxicity – ISO 10993-3

Genotoxicity testing evaluates gene mutations, changes in chromosomes or DNA and gene toxicities caused by by-products or compounds over an extended period of time. The International Organization for Standardization (ISO) standard 10993-3 outlines tests for genotoxicity, carcinogenicity and

reproductive toxicity. The ISO guidelines for genotoxicity testing require examination of gene mutation (bacterial mutagenicity test), chromosomal aberrations (chromosomal aberration assay) and DNA effects (mouse lymphoma assay). The FDA also requires three genotoxicity tests. The bacterial reverse mutation and the *in vitro* mouse lymphoma tests are the same as those recommended by ISO. A third test, which some within the FDA recommend, is an *in vivo* test, such as the mouse micronucleus test.

7.14.2 Carcinogenicity – ISO 10993-3

This test is performed only if there are data from other sources suggesting possible difficulties. The test needs to be performed over most of the test subject's life. It looks for tumorigenicity as well as chronic toxicity.

7.14.3 Reproductive/developmental testing – ISO 10993-3

This test is performed when there is concern that the reproductive system could be affected. It tests the effects of the material or implant on the reproductive system, embryo development, as well as pre- and post-natal development.

7.14.4 Haemocompatibility testing – ISO 10993-4

These tests evaluate the effects of product or compounds on blood or blood components, directly or indirectly during routine use. Haemocompatibility testing evaluates the effects on blood/blood components of blood-contacting devices/polymers. Thrombosis, coagulation, platelets, haematology, immunology are examined via simulation of geometry, contact conditions, flow dynamics, and blood reactivity differences between species via short- and long-term testing. The degree of haemolysis is measured spectrophotometrically.

The activation of complement proteins due to the use of a medical device has been associated with adverse clinical reactions. An enzyme immunoassay is used to screen for complement components in human serum that has been incubated with the test article. Elevated levels of complement components C3a and SC5b-9 indicate activation of the complement system. Both C3a and SC5b-9 assays are available.

One test determines the time citrated human plasma takes to form a clot, when it is first exposed to the test material, then to calcium chloride and, finally, to partial thromboplastin. Test results may report the 'partial thromboplastin time' (PTT) – that is, the time it takes the recalcified citrated plasma to clot

once the partial thromboplastin has been added. The test material is removed and examined for the presence of thrombi, and the vein is examined for patency (occlusion). These observations are complemented by photographs.

7.14.5 Cytotoxicity testing – ISO 10993-5

A cytotoxicity test determines whether a product or compound will have any toxic effect on living cells. These tests are typically used to test raw materials or components at the design stage and as a periodic test of material quality during production. These tests involve exposure of substances extracted from test material to one of two cell culture lines. Cytotoxicity *in vitro* testing is also used to ensure material biocompatibility. The ISO test method is used to meet international regulatory requirements. The USP test method meets the FDA's US regulatory requirements.

7.14.6 Implantation – ISO 10993-6

This test studies the effects of products or compounds on living tissue. Exaggerated amounts of material should be used. It is important to calculate the maximum amount of material that would be used and then implant multiples of that amount in an experiment. These studies help determine whether device surface characteristics, polymer composition and physical geometry affect local tissue responses, such as inflammation, tissue in growth, vascularisation and fibroplasia.

Acute inflammation can be characterised by: neutrophils of short life (hours to days); measurements of monocytes and macrophages at their highest concentrations; observations of exudation of fluid and plasma proteins; phagocytosis; and recognition, attachment, engulfment and degradation of foreign materials by leukocytes. Chronic inflammation occurs from persistent inflammatory stimuli such as macrophages, key mediators in immune reaction development which release growth factors. Other possible aspects are lymphocytes and plasma cells, antibody production, delayed hypersensitivity response, and there can be blood vessels and connective tissue proliferation related to an implant, localised at the implant site, caused by chemical and physical properties and/or motion device(s) or polymers. Gross and histologic photomicrographs can also be used.

7.14.7 Biodegradation – ISO 10993-9

These tests evaluate how much of the product or compound is absorbed by the body and follows the product or compound through the body after it has been absorbed to determine the effects over time.

7.14.8 Sensitisation – ISO 10993-10

This test evaluates sensitivity (e.g. allergic reactions) by the body to an implanted material or device. The murine local lymph node assay (LLNA), for example, has become a standard test method with good sensitivity and specificity, especially for delayed-type hypersensitivity when combined with statistical data analysis and negative control groups.

7.14.9 Irritation – ISO 10993-10

This test determines how irritable a product, material or compound is to the body. Studies should be made in combination with how the product or compound will be used and affected areas should be tested to determine the effect over time. For ocular, dermal and mucosal tissue contact, the appropriate test is selected. For breached tissue and blood contact, an intracutaneous test is chosen and typically uses only extracts. The dermal irritation test usually involves direct contact with the test material. The mucosal irritation test can involve either direct contact or use of extracts. The ocular tests usually use extracts. Extracts are prepared using solvents that will extract either hydrophilic (polar) or lipophilic (non-polar) compounds present in the device materials.

7.14.10 Acute systemic toxicity – ISO 10993-11

This test identifies the effect of exposure to a product or compound within 24 h. Acute toxicity occurs after a single exposure or repeated exposures to the test subject. Sub-acute symptoms appear within 14–28 days of delivery.

Acute toxicity tests estimate the potential harmful systemic effects from a single exposure to polar or non-polar extracts of device materials. Sub-acute toxicity is assessed after single or multiple exposures to extracts of device materials. The exposure period is longer than typical acute toxicity tests, but not exceeding 10% of animal's life span. Sub-acute studies involve expanded evaluations and can include systemic changes, local irritation, body weight, blood values and tissue changes as part of the protocol. The length of time for the test and the parameters evaluated depend on the end use of the device.

7.14.11 Sub-chronic toxicity – ISO 10993-11

Studies that continue for 90 days or for up to 10% of a test subject's life span are considered sub-chronic. Studies that continue for longer than 10% of a test subjects, life span are considered chronic.

7.14.12 Chronic toxicity – ISO 10993-11

Chronic toxicity studies can require that animal subjects be exposed to varying doses of test agents over long-term studies lasting two years or longer. If the device involves new chemistry that (from material characterisation and exposure assessments) indicates a high enough risk, one or more of these studies may be necessary. Chronic toxicity tests carried out over at least 10% of an animal's life span determine carcinogenicity or tumour-generating potential with single/multiple insults.

7.14.13 Summary

For implantable polymers that require special processing, the supplier or manufacturer should be contacted. A polymer used as a biomaterial in an implanted medical device must be proven to be non-toxic, biocompatible and safe to FDA and other regulatory standards before use. Material selection must meet the stringent requirements of ISO 10993-1[7] (see Table 7.10). The materials are tested after exposure to the sterilisation technique. The biological testing of the polymer is dependent on the intended contact duration. Body-contact polymers are characterised as surface contact, external communicating and implant. Implanted polymers have the most stringent requirements (see Table 7.10).

7.15 Conclusions

Studies found in the literature form the foundation for the work going forward, and they provide some good guidelines and insights. However, experience with real-world polymers shows a need for more careful and thorough evaluations. For example, potential polymer toxicity does not have the same response in older patients than younger patients, who often have biological repair mechanisms that older patients no longer have. In general, the trends point towards a need for a little less optimism and more careful understanding of the interaction between design, material selection, sterilisation, biocompatibility, environment and final polymer product performance.

Sterilisation is an important challenge and polymers known to be heat sterilisable and biocompatible have intrinsic long-term advantage. Heat sterilisation enables devices to be completely sterilised, is inexpensive, enables resterilisation, is more readily available and accessible in healthcare facilities. Heat sterilisation at lower temperatures will allow more heat-sensitive polymers to be sterilisable because the new sterilisation techniques are for niche applications, provide less penetration and are small scale. Heat sterilisation uses no toxic chemicals, does not generate toxic waste and is thus environmentally safe. Polymers and packaging materials continue to become more

Table 7.10 Initial evaluation tests for consideration

Device categories		Initial evaluation test (biological effect)								Supplementary evaluation test (biological effect)			
Body contact	Contact duration	Cytotoxicity	Sensitisation	Irritation or intracutaneous reactivity	System toxicity (acute)	Sub-chronic toxicity (sub-acute toxicity)	Genotoxicity	Implantation	Haemocompatability	Chronic toxicity	Carcinogenicity	Reproductive/ developmental	Biodegradable
Surface devices													
Skin	A	X	X	X	–	–	–	–	–	–	–	–	–
	B	X	X	X	–	–	–	–	–	–	–	–	–
	C	X	X	X	–	–	–	–	–	–	–	–	–
Mucosal membrane	A	X	X	X	–	–	–	–	–	–	–	–	–
	B	X	X	X	O	O	–	O	–	–	–	–	–
	C	X	X	X	O	X	X	O	–	O	–	–	–
Breached or compromised surfaces	A	X	X	X	O	–	–	–	–	–	–	–	–
	B	X	X	X	O	O	–	O	–	–	–	–	–
	C	X	X	X	O	X	X	O	–	O	–	–	–
External communicating devices													
Blood path, indirect	A	X	X	X	X	–	–	–	X				
	B	X	X	X	X	O	–	–	X	–	–	–	–
	C	X	X	O	X	X	X	O	X	–	–	–	–

(*Continued*)

Table 7.10 Continued

Device categories		Initial evaluation test (biological effect)								Supplementary evaluation test (biological effect)			
Body contact	Contact duration	Cytotoxicity	Sensitisation	Irritation or intracutaneous reactivity	System toxicity (acute)	Sub-chronic toxicity (sub-acute toxicity)	Genotoxicity	Implantation	Haemocompatability	Chronic toxicity	Carcinogenicity	Reproductive/ Developmental	Biodegradable
Tissue/bone/dentine communicating*	A	X	X	X	O	–	–	–	–	X	X	–	–
	B	X	X	O	O	O	X	X	–	–	–	–	–
	C	X	X	O	O	O	X	X	–	–	–	–	–
Circulation blood	A	X	X	X	X	–	O†	–	X	O	X	–	–
	B	X	X	X	X	X	X	O	X	–	–	–	–
	C	X	X	X	X	X	X	O	X	–	–	–	–
Implant devices													
Tissue/bone	A	X	X	X	O	–	–	–	–	–	–	–	–
	B	X	X	O	O	O	X	X	–	–	–	–	–
	C	X	X	O	O	O	X	X	–	X	X	–	–
Blood	A	X	X	X	X	–	–	X	X	–	–	–	–
	B	X	X	X	X	O	X	X	X	–	–	–	–
	C	X	X	X	X	X	X	X	X	X	X	–	–

Notes: X = ISO Evaluation tests for consideration; O = additional tests which may be applicable.
* Tissue includes tissue fluids and subcutanous spaces; † for all devices used in extracorporeal circuits.
Contact duration: A, limited (24 h); B, prolonged (24 h to 30 days); C, permanent (>30 days).
Sources: ANSI/AAMI/ISO 10993-1, AAMI, 2003.[7]

heat stable, heat sterilisable and less costly because of demand not only for medical devices, but also for other applications. In particular, heat-resistant fluoropolymers should provide cost-effective solutions to the ever-growing demands of biocompatibility and modern medical technology.

7.16 Sources of further information

Anand, V. P., *et al*. 2003. Re-evaluation of ethylene oxide hemolysis and irritation potential. *Journal of Biomedical Materials Research*, **64A**, 648–54.

Anes, J., *et al*. 1992. Use of plastics for parenteral packaging. In Avis, K. E., Lieberman, H.A. and Lachman, L. (eds), *Pharmaceutical Dosage Forms: Parenteral Medication*, Vol. 1, 2nd edn. Munich: Marcel Dekker, 387–444.

Berger, K. and Doriff, D. 2001. Efficacy and sterility in flexible packaging, *Medical Device & Diagnostic Industry*, Canon Communications, Los Angeles, CA, 1–8.

Canon Communications 2004. *Modern Plastics Worldwide World Encyclopedia: The Global Plastics Magazine*. http://www.modplas.com/worldencyclopedia/search, various pages of manufacturer information.

Czuba, L. 1999. Medical plastics for PVC replacement in medical solution containers, *Medical Device & Diagnostic Industry*, Canon Communications, Los Angeles, CA, 1–5.

Czuba, L. 2004. Polymers: paving the road of medical device progress, *Medical Device & Diagnostic Industry*, Canon Communications, Los Angeles, CA, 1–4.

Frissora, C. 2007. Trends in device design: implications for materials selection, *Medical Device & Diagnostic Industry*, Canon Communications, Los Angeles, CA, 9006, 4 80–90.

Gil, F. J., Gnebra, M. P. and Planell, J. A. 2002. Surface hardening by anodizing and heat treatments of Ti6Al4V alloys for articular prostheses. *Bio-medical Materials and Engineering* **12**(3), 271–81.

Hermanson, N. and Wessel, T. 1998. Syndiotactic polystyrene: a new polymer for high performance. *Medical Applications*, July, 1–4.

Hemmerich, K. J. 2000. Polymer materials selection for radiation-sterilized products. *Medical Device & Diagnostic Industry*, February.

Hui, H. K., Feldman, L. A., Timm, D. and Wu, S. 1999. Materials compatibility with low-temperature hydrogen peroxide gas plasma. *Infection Control Today*, May.

Lundy, C. 1994. Selecting polymers for medical devices. *Medical Plastics and Biomaterials*, Summer, 22–7.

Marino, F., Floyd, B. and Rogers, W. (technical assistance). 1992. Industrial Sterilization: a review of current principles and practices. In Avis, K. E., Lieberman, H. A. and Lachman, L. (eds), *Pharmaceutical Dosage Forms: Parenteral Medication*, Vol. 2. New York: Marcel Dekker, 1–54, 142, 155–215, 378.

Molin, G. 1977. Inactivation of bacillus spores in dry systems at low and high temperatures. *Journal of General Microbiology*, **101**, 227–31.

Modern Plastics (yearly) 1977. *Modern Plastics World Encyclopedia*, Modern Plastics, New York.

Perkins, J. J. 1970. *Principles and Methods of Sterilization in Health Sciences*. Springfield, IL: Charles C. Thomas, 54, 204, 261–2, 296–9, 301.

Plastics Design Library 1994. *The Effect of Sterilization Methods on Plastics and Elastomers*. Morris, NY: Plastics Design Laboratory.

Portnoy, R. 1997. Clear radiation, autoclavable polypropylene. *Medical Plastics and Biomaterials*, January, 1–9.

Rhodes, A. and Fletcher, D. 1996. Principles of sterilisation, sterility tests and asepsis. In *Principles of Industrial Microbiology*. Headington Hill Hall, Oxford: Pergamon, 45–57.

Rogers, W. 2005. *Sterilisation of Polymer Healthcare Products*. Shawbury, UK: RAPRA Technology.

Rubin, I. 1990. *Handbook of Plastic Materials and Technology*. New York: John Wiley & Sons.

Skeins, W. E. and Williams, J. L. 1983. Ionizing radiation's effect on selected biomedical polymers. In Szycher, M. (ed.), *Biocompatible Polymers, Metals, and Composites.* Society of Plastics Engineers, Technomic Pub. Co., Chapter 44: 1001–1018.

Steward, R. 2005. New polymers offer advantages for medical devices and packaging. *Plastics Engineering*, October 20–7.

Sturdevant, M. 1998. *Sterilization Compatibility of Rigid Thermoplastic Materials*. Dow Chemical Company Report.

Szycher, M. 1991. *High Performance Biomaterials*. Lancaster, PA: Technomic.

Williams, D. F. 1987. Tissue-bio material interaction. *Journal of Material Science*, **22**, 3421–45.

Williams, D. F. (ed.) 1981. *Fundamental Aspects of Biocompatibility*, Vols I and II. Boca Raton, FL: CRC Press.

7.17 References

1. American Association of Medical Instrumentation (AAMI) 2008. *Compatibility of Materials Subject to Sterilisation*, Technical Information Report (TIR) 17, AAMI, Arlington, VA.
2. Rogers, W. 2006. Steam: Uses and challenges for device sterilization. *Medical Device & Diagnostic Industry*, March, 80–7.
3. Rogers, W. 2005. *Sterilisation of Polymer Healthcare Products*. Shawbury, UK: RAPRA Technology, 97–134, 147–302.
4. Tang, F. W., Lambert, B. J. and Rogers, W. J. *Polymers in Medical Applications*. Shawbury, UK: RAPRA Technology, 1–15.
5. Plastics Design Library. 1994. *The Effect of Sterilization Methods on Plastics and Elastomers*. Morris, NY: Plastics Design Laboratory, 1–338.
6. Williams, D. F. (ed.) 1981. *Fundamental Aspects of Biocompatibility*, Vol. I. Boca Raton, FL: CRC Press, 46, 53.
7. Association for the Advancement of Medical Instrumentation 2003. *Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing*. ANSI/AAMI/ISO 10993-1, AAMI, Arlington, VA.
8. Association for the Advancement of Medical Instrumentation 2006. *Biological Evaluation of Medical Devices – Part 2: Animal Welfare Requirements*. ANSI/AAMI/ISO 10993-2, AAMI, Arlington, VA.
9. Association for the Advancement of Medical Instrumentation 2003. *Biological Evaluation of Medical Devices – Part 3: Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*. ANSI/AAMI/ISO 10993-3, AAMI, Arlington, VA.
10. Association for the Advancement of Medical Instrumentation 2002. *Biological Evaluation of Medical Devices – Part 4: Selection of Tests for Interactions with Blood, and Amendment 1:2006*. ANSI/AAMI/ISO 10993-4, AAMI, Arlington, VA.
11. Association for the Advancement of Medical Instrumentation 2006. *Biological Evaluation of Medical Devices – Part 5: Tests for* in vitro *Cytotoxicity*. ANSI/AAMI/ISO 10993-5. AAMI, Arlington, VA.

12. Association for the Advancement of Medical Instrumentation 2007. *Biological Evaluation of Medical Devices – Part 6: Tests For Local Effects after Implantation*. ANSI/AAMI/ISO 10993-6, AAMI, Arlington, VA.
13. Association for the Advancement of Medical Instrumentation 2001. *Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilisation Residuals*. ANSI/AAMI/ISO 10993-7, AAMI, Arlington, VA.
14. Association for the Advancement of Medical Instrumentation 2005. *Biological Evaluation of Medical Devices – Part 9: Framework for Identification and Quantification of Potential Degradation Products*. ANSI/AAMI/ISO 10993-9:1999/(R), AAMI, Arlington, VA.
15. Association for the Advancement of Medical Instrumentation 2006. *Biological Evaluation of Medical Devices – Part 11: Tests for Systemic Toxicity*. ANSI/AAMI/ISO 10993-11 AAMI, Arlington, VA.
16. Association for the Advancement of Medical Instrumentation 2007. *Biological Evaluation of Medical Devices – Part 12: Sample Preparation and Reference Materials*. ANSI/AAMI/ISO 10993-12 AAMI, Arlington, VA.