# Chapter 10
# Medical Device Manufacturing: Environment, Engineering Control and Monitoring

**R. Handy, M. Whitt, M. Lafreniere and M.J. Jackson**

**Abstract** The trend toward an aging population in the highly developed countries of the world has the demand for innovative biomedical devices and tools at record levels. The products desired in this market are typically smaller and more portable than their predecessors, and require more sophisticated components and allied manufacturing technologies and automation techniques. In essence, similar to traditional consumer products, biomedical devices such as patient monitors, drug delivery systems, therapeutic devices, and life assisting devices have all decreased in size yet still have market expectations of enhanced performance characteristics and features. This chapter focuses on medical device manufacturing from the environmental, engineering control, and monitoring perspectives.

## 10.1 Introduction

As a consequence of these market realities, many biomedical device companies have begun modeling their manufacturing environments in a similar fashion to the more traditional industries [1–35]. An example of a modern day portable medical device, an implantable pacemaker, is shown in comparison to its first generation predecessor in Fig. 10.1. A typical biomedical device manufacturing facility starting up today might include the capabilities for fine pitch component placement as a part of a high volume automation line, which is additionally equipped with the necessary advanced testing instrumentation to ensure product quality and assurance.

R. Handy
School of Medicine, The University of Utah, Salt Lake City, UT, USA

M. Whitt
California State Polytechnic, San Luis-Obispo, CA, USA

M. Lafreniere
Ohio University, Chillicothe, OH, USA

M.J. Jackson (✉)
Kansas State University, Salina, KS, USA
e-mail: jacksonmj04@yahoo.com



W. Ahmed and M.J. Jackson (eds.), *Surgical Tools and Medical Devices*,
DOI 10.1007/978-3-319-33489-9_10

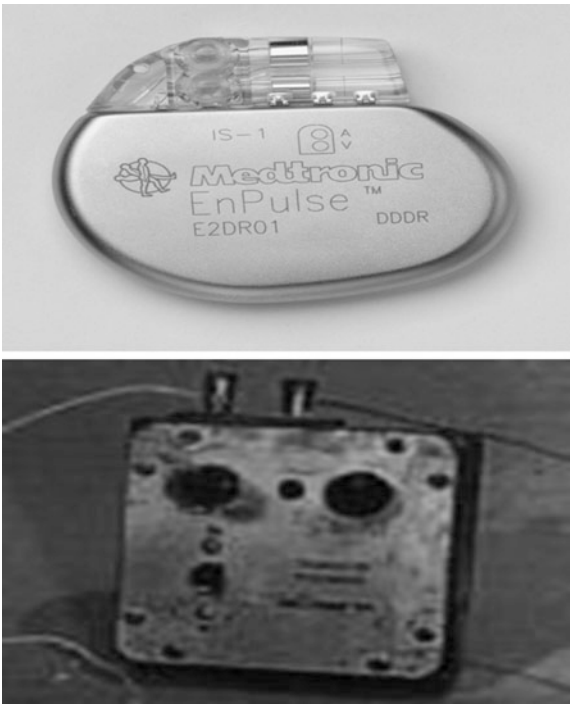


**Fig. 10.1** Modern implantable pacemaker (*left*) versus original portable external device (*Permission* Medtronics Canada and Minnesota Technology)

Unfortunately, as similarities increase in manufacturing design, it should also be expected that some of the negative consequences inherent to traditional manufacturing environments should become real issues as well in the biomedical device industry. One major area of concern must be the proper control and monitoring of environmental and worker exposures to potentially harmful chemical, biological, and physical stressors found in increasing concentrations in biomedical device manufacturing.

The purpose of this chapter is to present some of the strategies that could be employed to effectively control and monitor for workplace hazards associated chemical, biological, and physical agents in the biomedical device industry. This chapter begins with a presentation of a comprehensive list of the stressors found in the industry, with an overview of the properties, toxicity/exposure limits, and other pertinent characteristics of each, respectively. This chapter continues with an introduction to the typical environmental and engineering control methods and personal protective equipment (PPE) that should be implemented to help alleviate (or eliminate) the concern for any overexposures to any of these stressors [1–35].

## 10.2 Stressor Source, Properties, and Characteristics

It is expected that the biomedical device market will significantly grow globally over the next couple of years, with 34.5 % growth rates estimated in the nanoscale market alone through 2007 [1–35]. With the increased production rates brought on by these pressures, it can only be predicted that the use of additional chemical, biological, and physical agents associated with manufacturing these products will also rise substantially. Thus, it can easily be argued that an overall understanding by manufacturing personnel of the capabilities and limitations as well as the potential benefits and detriments of their usage should be imperative. This section attempts to delimit the list to pertinent stressors, with a detailed coverage for each provided on normal source and usage, chemical and physical properties, and toxicity characteristics. A comprehensive list of the stressors provided in this section and deemed the most commonly found in the biomedical device industry, along with source, properties, and toxicity characteristics for each, has been summarized in Table 10.1.

**Table 10.1** Common stressors found in biomedical device manufacturing

| Stressors | Source | Properties and toxicity characteristics |
|---|---|---|
| Ethylene oxide (EtO) | Sterilization | EtO is a colorless, flammable gas at room temperature and pressure with an ether-like odor, which has been linked to leukemia and peritoneal cancer. Acute exposures to >800 parts per million (ppm) can results in severe mucous membrane irritation and edema |
| Ionizing radiation (IR) | Sterilization, lab instruments | Ionization radiation exposures can be from primarily gamma ray, X-ray, beta particle, alpha particle, and electron beam exposures. Gamma and X-rays are the most penetrating, with beta particles being intermediate and alpha particles depositing energy over only a short traverse |
| Nonionizing radiation (NIR) | Sterilization, instruments, surface prep, cutting, etc. | The most common nonionizing radiation exposures will be from UV and lasers. UV can cause damage to the skin and eyes while laser energy primarily targets the eyes |
| Ozone | Welding, sterilization | Ozone is a colorless to blue colored gas at room temperature and pressure, with a very pungent odor. It is nonflammable but a powerful oxidizer that severely irritates the eyes, mucous membranes, and respiratory tract at levels greater than 5 ppm |

(continued)

**Table 10.1** (continued)

| Stressors | Source | Properties and toxicity characteristics |
|---|---|---|
| Hydrogen peroxide | Sterilization | Hydrogen peroxide is a noncombustible, colorless liquid with a slightly sharp odor. It is totally miscible in water and a powerful oxidizer with the potential to cause severe damage to the respiratory tract at concentrations greater than 75 ppm |
| Isopropanol (IPA) | Cleaning, disinfecting | IPA is a colorless liquid with the odor of rubbing alcohol. It is flammable and miscible in water with a vapor pressure of 33 mmHg. At concentrations greater than 4000 ppm, severe dizziness and drowsiness can occur in those exposed |
| Methanol | Cleaning | Methanol is a colorless, flammable liquid at room temperature and pressure with a characteristic pungent odor. It has a vapor pressure of 96 mmHg and is miscible in water with sever dizziness, drowsiness, and blindness occurring at levels greater than 6000 ppm |
| Ethanol | Cleaning | Ethanol is a colorless, flammable liquid. It has a vapor pressure of 44 mmHg and totally soluble in water. It can cause severe respiratory and CNS effects at concentrations greater than 1 % |
| Trichloroethylene (TCE) | Degreasing | TCE is a colorless, combustible liquid with a chloroform-like odor. It has a vapor pressure of 58 mmHg, a specific gravity of 1.46 (sinker), and 0.1 % solubility. At levels >1000 ppm, nausea, convulsions, and death can occur. Skin contact can lead to dermatitis |
| 1,1,1-Trichloroethane | Degreasing | 1,1,1-TCA is a colorless, combustible liquid with a mild, chloroform-like odor. It has a vapor pressure of 100 mmHg, a specific gravity of 1.34 (sinker), and 0.4 % solubility. At levels >700 ppm, severe respiratory tract irritation, poor equilibrium, and liver damage can occur. Skin exposures can lead to dermatitis |
| Acetone | Degreasing, cleaning | Acetone is a colorless, flammable liquid with a mint-like odor. It has a vapor pressure of 180 mmHg, is miscible, and has a specific gravity of 0.79 (floater). High airborne concentrations >5000 ppm can cause CNS depression. Skin exposures can cause dermatitis |

(continued)

**Table 10.1** (continued)

| Stressors | Source | Properties and toxicity characteristics |
|---|---|---|
| Perchloroethylene (Perk) | Degreasing | Perk is a colorless, noncombustible liquid with a chloroform-like odor. It is heavier than water, with a low solubility in water (0.02 %) and a low vapor pressure (14 mmHg). Exposures above 150 ppm can cause respiratory problems, dizziness, and liver damage. Exposures have resulted in liver tumors in animals |
| Hydrofluorocarbons | Degreasing | Hydrofluorocarbons are nonflammable solvents of very low toxicity. They are recyclable and have no effect on the ozone layer. However, emissions do contribute significantly to global warming |
| Hydrofluoroethers | Degreasing | Same as for hydrofluorocarbons |
| Perfluorocarbons | Degreasing | Same as for hydrofluorocarbons and hydrofluoroethers |
| Sulfuric acid | Etching, anodizing | Sulfuric acid is a strong corrosive liquid. It is colorless to dark brown in color, with little odor and an oil-like appearance. The target organs for this miscible, noncombustible liquid include the eyes, skin, and respiratory tract and the IDLH is 15 $mg/m^3$ |
| Nitric acid | Etching, anodizing | Nitric acid is a noncombustible and colorless, yellow, or red fuming liquid with an acrid, suffocating odor. It is miscible, with a vapor pressure of 48 mmHg. At concentrations >25 ppm, irritation to the eyes, skin, and respiratory tract can occur |
| Phosphoric acid | Etching, anodizing | Phosphoric acid is a noncombustible, colorless solid with no odor. It is miscible and causes skin burns and dermatitis on contact |
| Chromic acid | Etching, anodizing | Chromic acid is an odorless, noncombustible red solid, normally used in the flake or powder form. It is a known human carcinogen (septum/lung). Acute reactions include irritation of the respiratory tract and continuous exposures can cause sensitization dermatitis |

(continued)

**Table 10.1** (continued)

| Stressors | Source | Properties and toxicity characteristics |
|---|---|---|
| Potassium hydroxide | Etching, anodizing | Potassium hydroxide is a strong corrosive solid (pH > 13.0) with mainly skin and eye contact concerns. It is found as white or yellow lumps, flakes, rods, sticks, or pellets and in aqueous solutions. Inhalation exposures can be a concern if it gets airborne |
| Sodium Naphthenate | Etching, anodizing | Sodium naphthenate is a corrosive solid with mainly skin and eye contact concerns. It has a low vapor pressure and solubility in water and can be inhaled as an aerosol |
| Particulate matter | Surface prep, maintenance, welding, general activities, etc. | Particle matter has many sizes, shapes, and origins. It seems that those particles lesser than 2.5 μm have the most detrimental impact on human health. Inhalation of respirable particles can cause severe fibrosis and chronic manifestations such as silicosis |
| Polymer adhesives | Adhesive application | Exposures to airborne vapors from adhesives can lead to dizziness and headaches in those exposed. Many of the glues dry on contact and can negatively impact the skin and eyes |
| Heavy metal fumes and oxides | Welding and soldering | Chronic exposures to the various heavy metals can cause severe central nervous system malfunctions. Metal fumes have been linked to metal fume fever, with some metals such as cadmium and nickel classified as probable or known human carcinogens |
| Fluoropolymers | Surface coatings | Recent studies involving fluoropolymers support a linkage to cancer |
| Fluorides | Welding and soldering | Significant exposures to fluorides can lead to fluorosis, a severe condition that results in bone and enamel embrittlement |
| Acetylene | Welding | Acetylene is a very explosive gas that can also be a simple asphyxiant in high enough concentrations |
| Various aliphatic hydrocarbons | Coatings, adhesives | Dermal exposures to aliphatic hydrocarbons can lead to dermatitis. Hexane is the biggest airborne concern, however, most of those in this chemical group have relatively low toxicity. These are typically very flammable liquids |

(continued)

**Table 10.1** (continued)

| Stressors | Source | Properties and toxicity characteristics |
|---|---|---|
| Various aromatic hydrocarbons | Coatings, adhesives | Dermal exposures to aromatic hydrocarbons such as benzene, xylene, and toluene can dry out the skin and cause dermatitis. Benzene is a know carcinogen (blood cancer) and high concentrations can negatively impact the CNS and respiratory tract |
| Heat stress | Maintenance, some production | Heat stress can be an issue when personal protective equipment is being worn or when various hot working operations are being conducted |
| Noise | Maintenance, some production areas | Unhealthy levels of noise exposures are typically considered to be in excess of an average of 85 dB for 8 h or more in duration. Hearing protection is mandated at 85 or 90 dB |

The major manufacturing processes found in the biomedical industry that are related to this discussion can be generalized to the following categories:

1. Sterilization.
2. Cleaning, etching, and surface preparation.
3. Adhesive application.
4. Coating application.
5. Drilling, grinding, cutting, and other light production machining.
6. Welding and soldering.
7. General maintenance activities.
8. Laboratory research and testing.

## 10.3 Sterilization

Sterilization activities in the biomedical device industry are required by the European Union (EU) and the United States Federal Department of Agriculture (USFDA) and validation and routine control procedures are outlined in such documents as Association for the Advancement for Medical Instrumentation (AAMI)/International Organization for Standardization (ISO) 11135 for ethylene oxide sterilization and AAMI/ISO 11137 for radiation sterilization. There are literally dozens of ways to sterilize biomedical devices and new techniques are currently being developed and tested in research labs throughout the world. However, the most common methods of sterilization at this time are with ethylene oxide, gamma

rays, and electron beam radiation. The following paragraphs provide an overview of each of these as well as a few of the lesser used techniques (i.e., ozone, vapor phase hydrogen peroxide, plasma, microwave, and steam) and the associated health effects that could be realized if overexposed.

### *10.3.1 Ethylene Oxide Sterilization*

Ethylene oxide (EtO) is widely used as a sterilizing agent in the biomedical device industry, due primarily to its potency in destroying pathogens and material compatibility characteristics. It is estimated that nearly one-half of all medical devices produced are currently sterilized by EtO. EtO kills microbes by alkylation. Alkylation is the process by which EtO takes the place of the hydrogen atoms on molecules needed to sustain life. With enough time and concentration, this proves lethal to all of the microbial life that is present on the device.

Conventional wisdom would lead one to believe that if EtO is toxic to microbes, it would also likely be a human toxin. This is certainly the case. Ethylene oxide is a colorless gas at room temperature, with a flash point of below 0 °F and a flammability range of 3–100 vol.% in air. It has an ether-like odor and is considered a regulatory concern primarily due to its flammability and/or explosivity as well as its acute and chronic human toxicity characteristics. It is classified as a probable human carcinogen (A2), with a United States Occupational Safety and Health Administration (USOSHA) permissible exposure limit (PEL) of 1 ppm averaged over an 8-h shift and 5 ppm as a 15-min excursion.

The EtO sterilization process typically includes five steps: conditioning, sterilization, evacuation, air wash, and aeration. While human exposures to EtO during any of these stages is normally unlikely, there is always a chance of a process system leak or an operator making a deviation from the normal protocol or standard operating procedures. In addition, during setup and changeover periods, there is always a possibility of unsafe airborne exposures to personnel of this highly toxic gas. An illustration showing the precarious safety concerns involving the use of the EtO sterilization process is shown in Fig. 10.2.

### *10.3.2 Gamma Ray Sterilization*

Gamma rays, typically emitted from a source of cobalt-60 (Co-60), are also a common means for sterilizing biomedical devices. In fact, it is estimated that nearly 50 % of all single-use medical supplies (e.g., syringes, catheters, IV sets) have been sterilized by this technique. The gamma radiation emitted by the Co-60 source destroys any residual microbe by attacking the DNA of the molecules.

**Fig. 10.2** Illustration of ethylene oxide (EtO) leaking from a sterilization chamber (*Permission* Japanese Advanced Information Center for Safety and Health)

The main advantages using ionizing radiation to sterilize include optimal device penetration, process repeatability, and no product residues. And, from a health and safety standpoint, the typical, properly shielded cobalt-60 source has just enough energy to kill the microorganism of concern, but yet does not have enough energy to impart any harmful radioactivity to the surrounding workers or the environment. While the threat to overexposure to gamma radiation may be minimal to the biomedical device production worker, careful attention must be still taken to minimize the impact of any exposures and to always follow proper as low as reasonably achievable (ALARA) guidelines.

Cobalt-60 is solid substance that has a radioactive half-life of 5.27 years and decays by a beta/gamma scheme. Since it is gamma emitter, external exposures to large sources of this radionuclide can cause severe skin burns, acute radiation syndrome, and death. While careful safeguards have been put into place to prevent any worker exposures to ionizing radiation in the biomedical device industry, accidental emergency releases are always possible. Unlike EtO, the main regulatory responsibility for gamma radiation in the United States is not OSHA or the Environmental Protection Agency (USEPA) but the Nuclear Regulatory Commission (NRC). The acceptable annual dose limit for a nonnuclear energy worker in the U.S. is 1 mSv (100 mrem) dose equivalent while nuclear energy workers are allowed 50 mSv (5 rem) per year, with 100 mSv (10 rem) allowed accumulated exposure over a five-year period. The USOSHA PEL is currently set at 0.1 $mg/m^3$ for the nonradioactive component.

### 10.3.3 Electron Beam Radiation Sterilization

Another growing means for sterilization in the biomedical device manufacturing industry is by an electron beam radiation technique. Like gamma ray sterilization, this technique employs a beam of ionizing radiation that alters the DNA of the microorganism it attacks. Commercial electron beam accelerators range in energy from about 3–12 meV (million electron volts) and usually operate at only one energy level. The main advantages to this technique include shorter product exposure times, higher production rates, and less material oxidation.

One key aspect of both gamma ray and electron beam sterilization is the concept of dosimetric release. Dosimetric release is a procedure accepted by the USFDA and detailed in ANSI/AAMI/ISO 11137-1994. Dosimetric release is based upon readings from dosimeters placed on devices during processing. Verification of the minimum and maximum doses applied provides the mechanism for release and shipment. As will be discussed later in the monitoring section of the chapter, radiation dosimeters also provide useful information and control for worker health and safety biomedical device industry as well.

The same dose equivalent standards are used for electron beam sterilization as those in effect for the gamma ray techniques. USOSHA standards for ionizing radiation used in general industry can be found in 29 CFR 1910.1096. The EU regulations for ionizing radiation were set forth in the Council Directive 96/29/EURATOM of 13 May 1996.

### 10.3.4 Other Sterilization Techniques

While less common than those already addressed, device sterilization methods using ozone gas steam, plasma, vapor phase hydrogen peroxide, and microwave radiation have also been piloted in the laboratory and field settings. While proper safety controls have been normally put into place during circumstances employing one or more of these techniques, there is always a chance of an accidental release or a deviation from normal protocol that could result in an overexposure to either a single individual employee or a group of workers.

Ozone is a toxin that is a significant acute respiratory stressor. The immediately dangerous to life and health (IDLH) guideline for ozone is set a 5 ppm and USOSHA and ACGIH both set the occupational exposure limit for an 8-h shift at 0.1 ppm. In addition, USEPA regulates ozone emission to the environment and considers it to be one of the six National Ambient Air Quality Standards (or criteria pollutants), and the EU sets the ambient air standard for ozone at 0.12 mg/m$^3$. Hydrogen peroxide vapors are also considered toxic and most be controlled. The target organs for vapor phase hydrogen peroxide would be the eyes, skin, and respiratory tract, with a USOSHA PEL of 1 ppm established. Guidelines for non-ionizing radiation, including microwaves, are provided based upon various

frequency ranges and are delimited in such sources as ACGIH's TLVs for Chemical Substances and BEIs and the ICNIRP's General Approach to Protection Against Non-Ionizing Radiation. Regulations and guidelines for plasma processes are in the current research and findings stage and are not well established for worker health and safety.

## 10.4 Cleaning, Etching, and Surface Preparation

The effectiveness of the surface cleaning and preparation processes followed both during the manufacturing of the device as well as with the finished product will significantly impact the ultimate reliability and overall quality of the device in the field. For example, it is imperative that electronic medical devices have a clean surface in order to ensure good bonding and coating. In addition, compromised surface preparation can lead to the existence of chemical contaminants that can cause corrosion, and the non-removal of particulate matter may result in an undesirable electrical conductance path and short circuits.

Some of the most common cleaning processes used in biomedical device manufacturing include methanol, ethanol, isopropanol, chlorinated hydrocarbon solvents, fluorinated hydrocarbon solvents, acetone, and deionized water. Common etching or anodizing agents include sulfuric acid, phosphoric acid, chromic acid, sodium naphthenate, and potassium hydroxide. Mechanical surface preparations that many times cause unwanted particle residues and potential airborne contamination include surface and scuff sanding as well as grit blasting. Table 10.2 provides the target organs for each of these potential stressors and the approximate vapor hazard ratio (VHR), based upon the worldwide average occupational exposure limits (OELs), for some of the more commonly used solvents. The VHR, or vapor hazard index (VHI) as it is sometimes called, is found as follows:

$$\text{VHR (or VHI)} = C_{vp}/\text{OEL} \tag{10.1}$$

where $C_{vp}$ = concentration at the saturation vapor pressure in ppm and OEL = occupational exposure limit in ppm.

The VHR provides a convenient means for comparing the potential exposure impact to various solvents. Essentially, the VHR describes by how many times a saturated vapor volume must be diluted by this same volume of air so that the OEL is not exceeded.

### *10.4.1 Alcohols*

There are two types of surface contamination that are produced during the production of biomedical devices: polar and nonpolar. The majority of polar

**Table 10.2** Target organs and vapor hazard ratio (VHR) for selected chemical stressors

| Chemical stressor | Target organs [25] | Vapor hazard ratio |
|---|---|---|
| Isopropanol | Eyes, skin, and respiratory system | 100 |
| Methanol | Eyes, skin, respiratory system, and central nervous system (CNS) | 700 |
| Ethanol | Eyes, skin, respiratory system, CNS, liver, blood, and reproductive system | 75 |
| Trichloroethylene | Eyes, skin, respiratory system, heart, CNS, liver, and kidney | 1750 |
| 1,1,1 Trichloroethane | Eyes, skin, CNS, cardiovascular system, and liver | 800 |
| Perchloroethylene | Eyes, skin, respiratory system, liver, kidneys, and CNS | 550 |
| Acetone | Eyes, skin, respiratory system, and CNS | 450 |
| Potassium hydroxide | Eyes, skin, and respiratory system | – |
| Particulates (not otherwise regulation) | Eyes, skin, and respiratory system | – |
| Sulfuric acid | Eyes, skin, respiratory system, and teeth | – |
| Phosphoric acid | Eyes, skin, and respiratory system | – |
| Chromic acid | Blood, respiratory system, liver, kidneys, eyes, and skin | – |

contaminants found on biomedical devices during manufacturing include various inorganic compounds, with the source being primarily from flux activators or finger salts. Since alcohol is a polar compound and by taking into consideration the rule that "likes dissolve likes," the alcohols are many times used to remove polar contamination from the surface of biomedical devices. It has been a widely accepted premise that alcohol is the most effective and economical solvent available for removing ionic residues from biomedical devices, and thus, its use has grown concurrently with the increases in market demand over the years.

Employee exposure to airborne concentrations of alcohol can be irritating to the eyes, nose, and respiratory tract, with significant doses having been linked to manifestations of the central nervous system, liver, blood, and reproductive system. Obviously, efforts should be made to limit the exposure of alcohols to the employee's skin due to its solvent nature. Methanol is considered to be more toxic than both ethanol and isopropanol and its use should be limited under most circumstances.

However, as might be expected, methanol is deemed superior to the other two alcohols in the removal of significant ionic surface residues. Typical OELs have been set at 1000 ppm for ethanol, 200 ppm for methanol, and 400 ppm for isopropanol. The alcohols are not currently considered to be either a known or probable human carcinogen by any regulatory authority.

### *10.4.2 Chlorinated and Fluorinated Hydrocarbons*

Chlorinated and fluorinated hydrocarbons are used as nonpolar solvents in the industry. Nonpolar solvents such as methyl chloroform (1,1,1-TCA), trichloroethylene (TCE), and tetrachloroethylene (Perk) have been traditionally used because of their outstanding capabilities of removing oils, greases, rosin flux, etc., during the surface preparation process. However, requirements set forth by occupational and environmental regulatory authorities regarding these highly toxic and flammable compounds had increased the popularity of fluorinated solvents, chlorofluorohydrocarbons (CFCs), and various blends throughout the 1970s and 1980s. Still, with even more recent regulations, biomedical device producers have been dissuaded from using such fluorinated solvents such as trichlorotrifluoroethane. For example, Freon™, once a widely used industrial fluorochlorohydrocarbon, was identified as a major precursor contaminant that contributed significantly to stratospheric ozone depletion in the atmosphere, and thus, its use has been all but completely eliminated in most modern countries. As a matter of fact, the further production of this CFC in the U.S. was banned completely in 1996.

Today, the majority of biomedical device manufacturers use one or more of the following classes of nonpolar solvents in the production process to remove primarily oils and grease from the devices:

1. Hydrofluorocarbons (HFCs).
2. Hydrofluoroethers (HFEs).
3. Perfluorocarbons (PFCs) or perfluoropolyethers (PFEs).
4. Chlorinated hydrocarbons (e.g., TCE, Perk, 1,1,1-TCA).
5. *trans*-1,2-dichloroethylene.
6. Brominated solvents.
7. Hydrocarbons and oxygenated solvents.

The current trend for cleaning nonpolar compounds from the surface of medical devices appears to be moving away from the traditional chlorinated hydrocarbons and more toward HFCs and HFEs. These compounds are considered relatively benign in toxicity to animals and humans, however, are considered to be significant stressors to the environment, potentially enhancing global warming and greenhouse gas effects with a warming potential as much as five orders of magnitude greater than carbon dioxide gas.

As was mentioned previously, the chlorinated hydrocarbons are very closely scrutinized by both the environmental and occupational regulatory bodies due to both toxicity and flammability detriments. As would be expected, this family of chemicals affects the skin by removing all natural oils and potentially leading to severe dermatitis conditions. They are heavier than water and vapor pressures that range from 14 to 100 mmHg. The relative toxicity of the main three chemicals in the class (TCE, Perk, and 1,1,1-TCA) varies based on the concentration and the extent of the exposure (i.e., acute or chronic).

TCE is a colorless liquid with a chloroform-like odor, with chemical incompatibilities and reactivity to strong caustics and chemically active metals. The USOSHA PEL established for TCE is 100 ppm and has been linked to causing both liver and kidney tumors in animals. Along with the liver and kidneys, the main target organs include the respiratory tract and the central nervous system. The flash point for TCE is 160 °F, which classifies it as a combustible liquid.

Perk is a colorless liquid with a mild, chloroform-like odor and considered to be a strong oxidizer and incompatible with chemically active metals. It has an USOSHA PEL equal to 100 ppm and targets the liver, kidneys, respiratory tract, and central nervous system. Perk has been classified as animal carcinogen by causing liver tumors in test subject. While it is not classified as either a flammable or combustible liquid, it will decompose in the event of a fire to significant concentrations of hydrochloric acid (a corrosive vapor) and phosgene (a highly toxic gas).

Like both TCE and Perk, methyl chloroform (or 1,1,1-TCA) is a colorless liquid with a mild, chloroform-like odor, with incompatibilities to chemically active metals. It will also react with strong oxidizers, caustics, and water. 1,1,1-TCA targets the respiratory tract, skin, central nervous system, and liver but has not been linked to causing cancer in humans or animals. The EU OEL has been established for the stressor at 100 ppm and it is classified as a combustible liquid.

The majority of the HFCs, HFEs, PFCs, and PFEs do not have any occupational exposure established at this time. This is both due to the fact that these chemicals have been determined to be primarily nontoxic as well as their increased usage is a rather recent phenomenon, and thus, have not warranted up to this point much concern to the health and safety community. However, their collective effect on the environment, and particularly, on global warming impacts will undoubtedly be an issue to contend with as emissions are expected to only increase in the future. Figure 10.3 provides an example of a cell washer for in-line process degreasing.

### *10.4.3 Acids and Alkalis*

The primary acids used to surface etch biomedical devices include chromic, phosphoric, nitric, and sulfuric acid. Polymer surfaces are typically etched with a strong oxidizing agent such as chromic acid. The chromic acid provides the means to oxidize the substrate surface, resulting in an optimal surface for further treatments such as adding coatings or adhesives. Chromic, along with sulfuric and phosphoric acid, are many times employed as an etching or anodizing agent for metals such as titanium, stainless steel, and nickel. The surface preparation for fluoropolymers (or materials to be coated with fluoropolymers) is a difficult task. Treatments that have been effectively used in the industry include sodium naphthenate and potassium hydroxide etches as well as flame treatments.

Due to its highly acute and chronic toxicity, airborne and dermal chromic acid exposures to workers in the biomedical device industry must be of an utmost


**Fig. 10.3** Vapor degreaser used in biomedical device manufacturing (*Permission* Ramco, Inc.)

concern. Chromic acid has been linked to both human septum and lung cancer and is currently classified as a known human carcinogen. Since it is a strong acid, its corrosive nature can severely affect the respiratory tract as well as the skin of any exposed worker(s). Chromic acid is normally found in a red colored, aqueous solution in industry and is reactive with most readily oxidizable materials. The USOSHA ceiling exposure limit has been established for this chemical at 0.1 mg/m$^3$.

While the other acids typically used as etching and anodizing agents in biomedical device manufacturing are not considered known human carcinogens, they do exhibit comparable corrosivity. Thus, each of these agents targets the respiratory tract and the skin, with the possibility of severe burns being a reality upon even minimal exposure. The occupational limits established are 1 mg/m$^3$ for sulfuric, 5 mg/m$^3$ for nitric, and 1 mg/m$^3$ for phosphoric. Substance incompatibilities and reactivities include caustics (phosphoric), organic materials, metals, and even water (sulfuric and nitric).

Sodium naphthenate and potassium hydroxide are strong caustic etching agents used effectively on some polymer surfaces. Like their acid counterparts, they are very corrosive materials and target primarily the skin, eyes, and respiratory tract. They are not currently classified as probable human carcinogens and are typically found in industry in an aqueous solution. There is currently no USOSHA PEL or

EU OEL established for either of these agents. However, potassium hydroxide has a recommended TLV ceiling recommended by the ACGIH of 2 mg/m$^3$. These substances are reactive with acids, water, and metals.

### *10.4.4 Acetone*

Acetone is ubiquitous ketone solution used as a general purpose cleaning solvent in many industries. Its use varies in the biomedical device industry, with toxicity and exposure concerns typically minimal. The established EU OEL for this agent is 500 ppm, with incompatibilities existing between it and acids and oxidizers.

### *10.4.5 Particulate Matter*

Surface preparations such as sanding and blasting can cause the generation of particles and aerosols of various sizes, constituents, and morphology. Not only can their existence potentially compromise the quality and integrity of the completed device, but it can also be troublesome to those workers exposed to potential unhealthy airborne concentrations in their respective breathing zones. Depending primarily on the particle type and shape, there exists a myriad of factors that can be used to help determine the potential for negative impacts on employee health and well-being, both acute and chronic in nature.

Particulate matter is typically classified by aerodynamic diameters in the micron or submicron size ranges. Traditionally, any particles or aerosols of sizes less than 10 μm are considered to be respirable. Particulate matter greater than 10 μm in diameter is considered essentially benign because of the assumption that it will be eventually removed by other body defenses such as nose hair, cilia, and mucus before it reaches the inner respiratory tract. Due primarily to sufficient research on the exponential growth in adverse effects on human health from exposures to particulate matter in the 1–2.5 μm range, the USEPA has recently introduced a new tighter standard for ambient air exposures of this stressor.

Long-term exposures to some types of particulate matter found in the workplace have resulted in various forms of fibroses and pneumoconiosis (“dusty lung”) in otherwise healthy workers. Free silica from chronic exposures to sand has resulted in a chronic condition known as silicosis and exposures to airborne beryllium dust has initiated a manifestation known as berylliosis in those exposed. Recently, concerns have been expressed about the increasing exposures of workers in the biomedical device industry that may come into contact with airborne particles in the nanometer range. The human health effects from exposures to particles in the submicron ranges are not well understood at this time. Currently, USEPA considers

particulate matter as one of the six criteria pollutants and OELs in Spain have been set at 3 mg/m$^3$ for the respirable fraction. More stringent restrictions have been set for some particulate matter types that have been linked to chronic conditions such as fibrosis and cancer.

### *10.4.6 Spent Solvents*

Whether it is a benign substance like deionized water or a toxic substance such as chromic acid, once the agent has been used in the production process the resulting waste must be dealt with by following local and/or federal guidelines. The USEPA mandates a normal protocol to follow per RCRA and CERCLA provisions for hazardous waste generation and transport based upon the quantity generated. In the U.S., State-run EPA programs handle the management of wastes generated from "cradle to the grave." Depending on the jurisdiction, other countries, territories, provinces, and local governing groups may have different protocols to follow in order to effectively deal with their respective spent surface preparation agents.

### *10.4.7 The Future of Surface Preparation Techniques*

As have been previously discussed, most of the conventional cleaning methods and surface preparations have employed wet chemical techniques. However, the current trend seems to be moving away from chemical treatments and toward such modern techniques as cold plasma, corona discharge, and laser cleaning.

Corona discharge is a process by which high voltage electricity is discharged into an airstream, producing large concentrations of ozone to the oxidize the device surface while plasma cleaning employs an ionized, equally charged oxygen gas stream to chip apart the surface contaminants. Laser cleaning is still yet another recent technology used in the industry. Lasers are, of course, a concentrated form of light energy and are considered nonionizing in nature. The employee exposure concerns of various lasers will be covered in greater detail later on in this section.

Essentially, the health and safety concerns for workers in this environment have been switched from chemical stressors, for the most part, to physical stressors such as electricity, electrical/magnetic fields, and nonionizing radiation. Figure 10.4 provides an example of the plasma cleaning device that might be implemented in the biomedical device industry while Fig. 10.5 shows a laser cleaning method in use.


**Fig. 10.4** Plasma cleaning apparatus (*Permission* UCP Processing Ltd.)

**Fig. 10.5** Laser cleaning operation (*Permission* Adapt Laser Systems)

## 10.5 Adhesive Applications

Many of the previously discussed surface preparation techniques were completed in order to effectively and efficiently apply adhesives to various device substrates. While various mechanical fasteners as well as welding, brazing, and soldering techniques can be used to join many biomedical device materials together, there are still other materials, such as thermoplastic and thermosetting polymers, that are considered incompatible to these types of joining processes. Adhesive bonding conditions include:

1. Bonding of dissimilar materials.
2. Joining to promote optimal stress distributions or impact resistance.
3. Joining of very thin materials.
4. Joining of outsourced subassemblies.
5. Bonding for mechanical joint augmentation.

The most common adhesives used in biomedical device manufacturing include urethanes, cyanoacrylates, acrylics, epoxies, and silicones. Collectively, the adhesives primarily attack the skin, eyes, and respiratory tract. While sometimes quite odiferous, their vapor pressures are usually very low and most do not contain ingredients that are carcinogenic. Some of adhesives have components that are recognized as chemical sensitizers, and exothermic polymerization is always a concern if they should ever come into contact with incompatible materials. OELs have not been established specifically for any of these polymer groups but yet exposure standards have been determined for any hazardous ingredients that might be used as a product component.

The commercially available urethanes have a variety of ingredients; however, common to most products will be less than 5 % isocyanates and 5 % naptha. They are not carcinogenic but have been classified as chemical sensitizers, and overexposures can cause severe respiratory tract ailments including pulmonary edema and bronchitis. In case of a fire, urethane-based decomposition products of concern include carbon monoxide, nitrogen oxides, hydrochloric acid, and trace amount of hydrogen cyanide. Cyanoacrylates (or the "superglues") are eye and mucous membrane irritants and tissue bonders. Their vapors are lachrymatory and, if decomposed during a fire, produce a dense, choking smoke. They are incompatible with water, alcohols, and amines, sometimes producing a significant exothermic polymerization event.

The majority of the acrylic adhesive formulations used in biomedical device manufacturing can cause skin dermatitis as well as allergic reactions for those sensitive individuals. At high processing temperatures, it is possible for some employees exposed to acrylic adhesives to exhibit flu-like conditions known as "polymer flu." As for the epoxies, the main health and safety concerns include skin, eye, and respiratory tract irritation and chemical sensitization while silicone formulations being irritants which many times have a major toxic aliphatic or aromatic hydrocarbon component such as n-heptane or xylenes.

## 10.6 Coating Applications

The most common coatings applied to biomedical devices are urethane-based, fluoropolymers, or polyimide laminates. The techniques with a proven track record for device surface coating vary in sophistication and applicability. Depending on the type of material, as well as product size and configuration, one technique may prove to be more effective than another in ensuring coating quality and repeatability. The required coating thickness is also a major factor in the decision process. In any case, the coating techniques employed have the potential of producing aerosols of varying sizes and shapes of which significant employee exposures could be realized.

Since the majority of the coatings are polymer-based, many of the health and safety concerns with coatings are shared with the common adhesives that were discussed in the previous paragraphs. However, what differs significantly is the potential for toxic aerosols to build up to a significant concentration in the employee breathing zone during the specific coating application.

Like adhesives, there are certainly concerns for employee skin and mucous membrane exposures to the common coatings applied. Additionally, they can be chemical sensitizers and have other toxic ingredients in their formulation. However, what differs substantially between the two involves the potential for exposures to harmful levels of particulate matter and toxic metal pigments that can be inhaled by the associated production worker. Heavy metals linked to human cancer, such as chromium and cadmium, are used to provide color to many industrial coatings. Another major health concern related to biomedical device coating applications involves fluoropolymers such as Teflon®, which is a very common device coating due to its biocompatibility. Recent studies have linked fluoropolymers to increased incidences of cancer and teratogenesis for those exposed to a particular raw material, perfluorooctanoic acid (PFOA), used in its production, yet claims are still very controversial.

## 10.7 Drilling, Grinding, Cutting, and Machining

Drilling, grinding, and other light machining operations produce fine and course particulate matter, as well as significant concentrations of aerosols from the use of cutting oils and fluids. These particles range from just a few nanometers to well over 10 μm in sizes. Exposures to particles from the near micron range to around 10 μm have resulted in various lung ailments such as bronchitis, emphysema, anthracosis, and silicosis. The kinetics of these particles is pretty well understood and related health effects data is rather complete. However, the effects on human health of particles in the ultrafine particle size region of 100 nm, or less, is not well understood. As a matter of fact, the particles generated in this region behave more like gases than they do particles with regard to motion and kinetics.

While recent efforts have been directed toward removing from manufacturing many oils and cutting fluids with toxic ingredients and replacing them with human and environmentally friendly alternatives, there are still a vast amount of these necessary lubricants available for use in the biomedical industry. While there are an increasing number of aqueous-based fluids becoming commercially available, many of these lubricants are still petroleum-based, with the associated ill effects related to overexposures to aliphatic and aromatic hydrocarbons still a daunting reality.

Traditional cutting techniques also produce particulate matter and aerosols in the micron and submicron ranges. However, advanced techniques, such as laser cutting, have been piloted in the field and gaining popularity.

### *10.7.1 Laser Cutting*

Lasers are used for cutting in many manufacturing industries and the biomedical industry is no exception. Additionally, lasers can be found in welding, sealing, and coating operations as well as in medical micromachinery, lab instrumentation, and in the final device itself. Thus, a discussion on the environmental, health and safety issues regarding its proper use is imperative.

Lasers and laser equipment may be potentially dangerous to eyes and skin of the employee. The relative degree of risk depends on the type of beam, the power frequency, beam divergence, beam intensity, and duration of exposure. The eye is the most susceptible to damage, with retina burns resulting in the possibility of total blindness. Given certain levels and wavelengths of laser radiation, coupled with adequate duration, skin reddening, swelling, blistering, and even charring can occur.

Exposure guidelines are based on the characteristics of the type of laser and are expressed as maximum permissible exposure or MPE. The guidelines most often used involving the safe use of lasers has been published by ANSI, ACGIH, ICNIRP, and IEC [20]. Traditionally, the USFDA has used a laser classification scheme using four roman numbers I, II, IIIa, IIIb, and IV. The Class I laser was considered the most benign and eye safe, whereas the Class IV was the most dangerous for eye and skin exposures. However, the USFDA and ANSI and other industrialized countries are currently in the process of adopting, if they have not already done so, the International Electrotechnical Commission standard, IEC 60825-1. Table 10.3 summarizes the laser classes, with power, duration, and relative hazards provided. It should be pointed out that the “M” designation after the class is for “magnification” while the “R” is for “reduced requirements.”

**Table 10.3** Laser classification scheme and characteristics

| Laser class (IEC) | Laser class (old US FDA) | Allowable power (W) | Emission duration (s) | Hazard description |
|---|---|---|---|---|
| 1 | I | 0.39E−60 | >10,000 | Not a known eye or skin hazard |
| 1M | I | 0.39E−60 | >10,000 | Eye safe with no optical aids |
| 2 | II | <1.0E−3 | >0.25 | Potential eye hazard for chronic viewing |
| 2M | IIIa (low irradiance) | <5.0E−3 | >3.8E−4 | Potential eye hazard for chronic viewing and may be so with optical aids |
| 3R | IIIa (high irradiance) | <5.0E−3 | >3.8E−4 | Marginal hazard for intrabeam viewing |
| 3B | IIIb | <5.0E−1 | >0.25 | Known intrabeam viewing hazard |
| 4 | IV | >0.5 | NA | Known eye and skin hazard |

## 10.8 Welding and Soldering

Welding and soldering activities can sometimes pose an exposure risk for those not wearing the proper PPE and using adequate ventilation control. The main hazards associated with soldering include skin burns and airborne contaminant exposures, primarily from the solder, soldering flux, and any surface pre- or post-cleaning solutions. The primary welding hazards include exposures of air contaminants from sources such as the base material, welding rod, welding flux, and inerting gases. Potential physical hazards encountered during the process include nonionizing radiation, heat stress, and electricity.

Traditionally, the biggest concern for occupational solderers was the likely exposures to significant concentrations of lead in the air. Lead is an extremely acute and chronic toxin linked to a myriad of potential manifestations. Fortunately, most of the lead-based solder has been removed from manufacturing in the developed countries. However, exposures to the fumes generated from solders even without lead should be kept to a minimum. Many formulations of solder flux provide a substantial potential for unhealthy doses of fluorides. Additionally, normally low vapor pressure cleaners used during the process can become heated and emit higher than normal levels of gases and vapors into the breathing zone of the biomedical manufacturing worker.

Depending on the type of welding and the level of engineering controls implemented, a wide range of contaminant exposures can be realized. Airborne levels of ozone, nitrogen oxides, and fluorides are normally troublesome and heavy metal fumes of varying types and concentrations may also be of paramount concern. Typical metal fumes and oxides include iron, zinc, copper, cadmium, aluminum, magnesium, nickel, chromium, and manganese. The majority of these heavy metals are considered to be chronic toxins, targeting the central nervous system and lungs, and several of these toxins are either known or probable human

carcinogens. Exposures to heavy metal fumes have resulted in a condition known as "metal fume fever."

Workers must be shielded from the nonionizing radiation exposures possible from some welding processes. Harmful, high-frequency ultraviolet radiation has caused a manifestation known as "welder's flash" in some welders and vicinity workers. The symptoms of this condition include visual impairment, the feeling of sand or grit in the eye, and a severe headache with malaise. Additionally, welding should never be conducted near chlorinated cleaning solvents due to the potential of sparks initiating dangerous phosgene gas accumulations. Of course, burns and electrical shock are additional possible physical stressors of which the biomedical device production welder may become exposed.

## 10.9 General Maintenance Activities

There is a plethora of general maintenance activities possible at each respective biomedical device manufacturing facility, with many of these activities such as welding, drilling, cleaning, etc., having already been covered in the preceding paragraphs. However, the severity and the distinct nature of some of these tasks have merited a separate discussion.

Maintenance activities differ from those in normal production in potentially several ways. For one, the maintenance activities are many times not planned some time in advance before the actual event occurs. This means that exposures to non-expecting workers may be intensified. Second, maintenance activities that create potential environmental stressors are normally completed in a shorter duration, with higher activity levels and robustness. Thus, the potential for exposures is once again enhanced. Finally, maintenance and set-up activities many times lead to process control changes that may, after completion, result in unusual and significant short-term exposures to physical and chemical agents by area production workers.

Machining activities accomplished by maintenance workers sometimes produce noise levels that exceed the occupational limits and heat stress can also be of concern. Increased maintenance activities can produce airborne contaminants such as particulate matter/fibers and noxious gases, vapors, and fumes. Obviously, many the activities of facility maintenance personnel can produce unsafe slip, trips, and falls as well as electrical wiring and pneumatic/hydraulic plumbing concerns for all associated workers.

## 10.10 Laboratory Research and Testing

The research and quality control laboratories in the biomedical device manufacturing industry provide a rather unique environment for employee exposures. Lab technicians are typically working with a wide range of instruments with a variety of

operational characteristics and potential to exposures from various biological, chemical, and physical stressors. Instruments found in the laboratory environment include, among others, sources such as X-rays, gamma ray, lasers, and some wet chemistry components that could be harmful if not properly controlled.

While concerns involving biological stressors are possible in any of the before mentioned areas or during certain previously discussed activities, the research and quality control laboratories are the places where pilot runs are conducted and final devices are tested for contamination. Experimental procedures might include such activities as biocompatibility testing, with uses of bloods and other body fluids common. Depending on the device, ISO clean room status may be desired at a certain level in the labs as well as on the production floor; thus, various testing for bacteria and fungal contamination may be required. While there are currently no occupational mandates for personal exposure to most biological agents, governmental agencies on the environment and food and drugs have set some standards for microbial contamination.

## 10.11 Environmental and Engineering Controls

Administrative actions, engineering controls, and PPE are considered as the three main approaches to controlling environmental emissions and employee exposures. The intent of this section is to elucidate the common environmental and engineering controls that could be implemented in the biomedical device manufacturing climate to help protect the employee and the environment. Any of the following implemented individually or in combination are viable engineering control techniques that could work in the biomedical device industry:

1. Substitution.
2. Process controls (continuous or automation).
3. Enclosure/isolation.
4. Process elimination.
5. Process change.
6. Ventilation controls (local exhaust or dilution).

While prevention is not included as one of the above environmental and engineering controls, it should always be the first consideration taken when there is the potential for employee exposure to chemical, biological, and/or physical stressors. In essence, the control assessment should always begin with an evaluation of whether or not the situation that apparently requires control can just be totally prevented instead by some means.

Once the condition that has the potential to adversely impact human health or the environment has been recognized, then a proper controls implementation scheme should be followed. An effective protocol should be systematic and involve a series of steps taken to identify and characterize the hazard, exposure source, worker

involvement, and air movements, as well as identifying all alternatives, with the ultimate goal of implementing and testing/maintaining the best of these alternatives.

## 10.12 Substitution

Substitution is the process by which a more environmentally friendly substitute is made for a known hazardous substance, process, or piece of equipment. For example, it has been argued that the plasma cleaning process is superior to organic solvent cleaning when it comes to the potential for harmful exposures and negative human health impacts. Another example of substitution in the biomedical device industry might involve the use of lab instruments that employ sensors which work on the principal of nonionizing radiation instead of their predecessors, either gamma or X-ray radiation, which have more damaging characteristics on the cellular or tissue levels.

One must be careful that the substitution made does not result in such an inferior replacement to the original product, process, or equipment that it might compromise the quality and integrity of the final device. An example of this undesirable event might include a process/material change by a company from a nonpolar solvent to the use of a surfactant and water to clean a particular medical device, resulting in ineffective removal of contamination. Economics can also limit the benefits of substitution. For instance, while many biomedical companies have realized successes by substituting automated processes for those that were once somewhat labor intensive, others have failed to accomplish this goal. Quite frequently, this is due to the significant up-front costs associated with automation and the inability of the company to reach any economies of scale because of their size.

## 10.13 Process Controls

There are times when the current process controls need to be evaluated for their merit. As a general rule, intermittent or batch processes are typically considered to be more hazardous than those that are more continuous in nature. In essence, the automated line takes some of the human component out of the process, and thus, typically also reduces the potential for human exposures. However, as was discussed in the previous subsection, automated processes can have their own set of downfalls and shortcomings.

## 10.14 Enclosure/Isolation

The use of enclosures and isolation techniques will be found in almost all biomedical device manufacturing facilities. The sophistication of these control alternatives varies widely, with the intent to separate the potentially exposed employee from the hazardous event. A very good example of a type of enclosure being used in the industry is the glovebox setup. These units are found in a myriad of operations to protect the worker from the workpiece and process during applications of various physical, biological, and chemical stressors. For example, a glovebox apparatus might be used in the laboratory of a facility to test a particular medical device's biocompatibility or potential for rapid oxidation when coming in contact with a substance. Another common enclosure used in the industry is the particle and fume hood, typically required to keep microbial and particle concentrations at levels to meet or exceed ISO clean room standards.

The principle of isolation can be by either space or time. The use of walls or complete rooms to separate employees from a potential hazard, of course, is an example of the former. In contrast, conducting a special cleaning operation to remediate facility mold contamination on either the weekend or overnight would be an excellent example of the latter. Table 10.4 provides some examples of potential enclosure or isolation techniques that could be used effectively in biomedical device manufacturing.

**Table 10.4** Enclosure/isolation techniques used in biomedical device manufacturing

| Type of medical device or process | Enclosure/isolation technique |
|---|---|
| Co-60 use in teletherapy | Operator kept at safe distance from source and lead shielding from gamma radiation |
| Irradiator for instrument sterilization | Lead shielding with operator in a secured room |
| Ethylene oxide use for device sterilization | Specialized containment and time without employee in close proximity |
| Use of biological agents in the laboratory for testing | Glovebox with proper hazard classification characteristics |
| Radioactive iodine syringe preparation and assembly | Syringe shields and Plexiglass™ shielding for beta radiation during preparation |
| Acid etching of the substrate on devices and tools | Special acid enclosure and fume hood use |
| Controlled storage of chemicals | A regulatory-approved chemical storage cabinet |
| Automated production line | Clear acrylic safety shields to protect worker from moving parts and potential stressors |

## 10.15 Process Change or Elimination

Sometimes it is possible to change a process to make it less hazardous to the employee. For instance, a surface coating application could be applied through a dipping process rather than one that requires spraying. This change could eliminate the majority of the coating aerosols from ever entering the breathing zone of the worker. Additionally, the dipping process should be considerably more manageable from the aspect of environmental control and regulatory affairs.

It is even possible that a process of concern could be completely eliminated. Given our coating application example, it might be possible to eliminate the coating operation or simply apply a much thinner layer of coating using isolation and an advanced nanotechnology technique. Fortunately, many studies in general industry show that process changes (or eliminations) made in order to increase hazard control have actually resulted in enhanced productivity, as well as an improvement in overall product quality.

## 10.16 Ventilation Controls

A discussion on environmental and engineering controls would not be complete without a significant effort being put on covering the proper design, development, and implementation of the site ventilation system(s). Without adequate ventilation, there would be, in many cases, no other alternative but to put workers on respirators to eliminate their exposure potential. This is an issue that most companies should try to avoid; mandating respirators for protection complicates production and regulatory matters and adds a significant cost to the company. Fortunately, the use of proper ventilation will eliminate the necessity for respirator use by most biomedical device production workers during their normal work-related activities.

There are two types of ventilation: dilution ventilation and local exhaust ventilation (LEV). Most facilities have both of types of ventilation, with additions and changes to these networks occurring at least periodically, if not frequently. The following paragraphs attempt to elucidate the benefits that can be realized in controlling the production environment with an optimally designed ventilation network.

### *10.16.1 Dilution Ventilation*

Dilution ventilation, also known as general exhaust ventilation, controls the level of airborne stressors by removing the potentially contaminated air and replacing it with fresh dilution air before concentrations reach unhealthy levels. Under certain assumptions and constraints, the resulting equilibrium concentration of any airborne

contamination can be estimated as follows: C = E/Q, where C is the concentration, E is the emission rate, and Q is the ventilation rate.

Traditionally, ventilation experts have used the units of air changes per hour to express dilution ventilation exchange rates, and the notion of an "acceptable concentration" has been used to indicate a safe or comfortable level of exposure. Since a heavy reliance on adjacent sources of outdoor air for dilution exists, it is a must that this fresh air source has less contamination than what is realized on the production floor. Therefore, careful attention must be given to where air intakes are located to minimize the effects from outdoor sources of such ambient air contaminants as ozone, sulfur dioxide, particulate matter, and nitrogen dioxide. Also, during summer and wet months of the year, the dilution air could have significant levels of mold spores that could be brought into the biomedical device manufacturing environment.

Obviously, relying solely upon dilution ventilation to control airborne contaminants in the biomedical device manufacturing can be problematic. It is important to evaluate the potential for various stressor exposures and the relative toxicity of each of these. Inevitably, there will be some operations conducted during the development, testing, and manufacturing of a device that will not allow for engineering control only through dilution ventilation efforts. The use of dilution ventilation independently as a means for environmental and engineering control should be avoided if the following conditions exist:

1. The contaminants realized are highly toxic chemical, biological, or physical stressors.
2. The concentration levels are higher than established action levels or guidelines.
3. The emission rates are variable.
4. There exist only a few, high concentration discharge points for any contaminants.
5. The outdoor air might be suspect for various reasons.
6. The existing HVAC system is not adequate to provide "controllable" dilution air.
7. The worker's breathing zone is in close proximity to the emission point(s).

### *10.16.2 Local Exhaust Ventilation (LEV)*

LEV is many times coupled with effective dilution ventilation to keep airborne contaminant levels down to acceptable concentrations. The LEV commonly employs the use of a properly dimensioned hood, plumbed with the necessary ductwork to a series of mechanical components, with its endpoint being an emissions stack. At a minimum, a properly designed LEV will have an air cleaning device capable of removing the stressor(s) of concern as well as a fan designed to drive the air of the given volume and desired flow rate. Figure 10.6 shows the components of a typical LEV system.

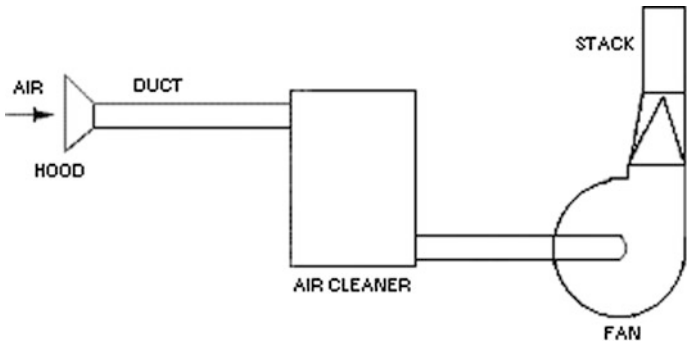


**Fig. 10.6** Components of a local exhaust ventilation (LEV) system

The LEV is the primary means for removing gases, vapors, fumes, and particles from the immediate breathing zone of workers in the biomedical device manufacturing industry. It is called "local" exhaust ventilation because the physical location of the system is always in the immediate proximity of the point source emission. In essence, the face of the hood is placed close enough to the workpiece/process to allow for the suction created from the mechanical fan to capture the contaminant and remove it up and out of the associated ductwork. Consequently, it has been written that capturing and removing an airborne stressor, such as an acid etchant vapor or a hydrocarbon solvent vapor, at its source is the principle objective of LEV systems. Typical operations that merit the use of LEVs in the industry include solvent cleaning, acid etching, sterilization, welding, soldering, coating applications, adhesive applications, clean room/laboratory activities, and any other industry-specific operation that produces point source air emissions.

A variation on the traditional LEV, commonly found in the biomedical device industry, is the kind designed specifically to meet international clean room standards for particulate and microbial contamination. In reality, this type of environmental and engineering control is really a combination of both LEV and a form of isolation/enclosure. Unlike the traditional units, the clean room system not only protects the worker from any stressor that may be inside its hood, but also serves the dual purpose of protecting the device/process from any external stressors, which if allowed to be present, could contaminate or corrupt. Many of these types of control devices are of the ductless variety, with installed high efficiency particulate air (HEPA) or ultralow penetration air (ULPA) filters to effectively collect and remove any airborne particles.

The local exhaust hood, in a broad sense, is any suction opening that is intended to draw the contaminant into the control system. Generalized, the three basic types of hoods are capture, enclosing, and canopy. Two important parameters unique to the local exhaust hood are the face velocity and the capture velocity. The face velocity, quite simply, is the air velocity at the hood opening. In contrast, the capture velocity is the air speed at any point in front of the hood (or at the hood opening) required to overcome any opposing air currents and capture the

**Table 10.5** Approximate hood capture velocities (adapted from NSC and ACGIH vent manual)

| Conditions of contaminant release | Approximate capture velocity in m/s (fpm) | Examples of processes or operations in biomedical device manufacturing |
|---|---|---|
| Release with no significant velocity into quiet air | 0.25–0.5 (50–100) | Degreasing, cleaning, etching, anodizing, adhesive application |
| Released with low velocity into moderately quiet air | 0.5–1.0 (100–200) | Coating applications, welding, and soldering |
| Released with considerable velocity or into area of rapid air movement | 1.0–2.5 (200–500) | Light surface preparations, some spray coatings, and machining operations |
| Released with high velocity or into zone of rapid air movement | 2.5–10 (500–2000) | Some maintenance operations, grinding, and other heavy machining operations |

contaminated air, causing it to flow into the hood. The point in space at which this occurs is called the capture point. Other velocity parameters important to proper hood and LEV design include slot velocity, plenum velocity, duct velocity, and minimum design duct velocity. Table 10.5 provides approximate capture velocities required to properly remove common contaminants found in the biomedical device manufacturing.

Normal capture velocities vary widely in the industry and are based mainly on the spatial characteristics of the LEV system and process interface as well as on the physical and chemical properties of the contaminant(s). Normal face velocities found on hoods in the biomedical device manufacturing industry usually are in the range of 80 feet per minute (fpm)–100 fpm.

After the contaminated air has been captured by the local exhaust hood, the ductwork serves as the carrying conduit on to the other mechanical components of the LEV, and finally, on up the stack and out. The ducts are typically made from sheet metal, with rectangular or circular cross sections of varying dimensions. The mass flow of contaminated air in a duct system is based on the duct velocity and the cross-sectional and can be calculated as follows: $Q = v/A$ where Q is the mass flow, v is the duct velocity, and A is the cross-sectional area. Typically, the economically optimal duct velocity found for systems in the biomedical device industry ranges from 1000 fpm for most cleaning, etching, and adhesive application processes up to around 2000 fpm for some welding or soldering operations. The maximum duct velocity that could possibly be encountered in the industry would be for heavy maintenance and machining operations, where velocities may reach as high as 4000 fpm.

Three critical parameters that require an understanding when calculating and controlling duct velocities include the static pressure, the velocity pressure, and the duct friction losses. The static pressure is the energy source of the system and is created by the fan while the velocity pressure is the pressure creating by the air in flux. It can be said that velocity pressure is what is realized by converting static pressure into air movement within the duct. These important parameters are

typically measured by performing what is known as a pitot traverse. Friction losses (and other losses) must be considered for optimal LEV system design, and values for these losses are based on such characteristics as length, diameter, and configuration. Values for LEV duct friction losses can be found tabulated in various sources including manufacturer specification sheets.

Air cleaners are a necessary component of a properly designed LEV system. Some of the more commonly found types of cleaners commercially available include:

1. Electrostatic precipitators.
2. Simple setting chambers.
3. Wet and dry centrifugal collectors.
4. Venturi scrubbers.
5. Washers.
6. Fabric filters (e.g., HEPA or ULPA).
7. Packed tower or scrubber.
8. Carbon adsorption.
9. Catalytic units.

The type of cleaner chosen for the LEV system must be able to effectively remove the contaminant of concern. Thus, the type of cleaner capable of removing particulate matter at a known efficiency will be more than likely considerably different from one which is effective at removing a vapor or fume. Along with the nature of the contaminant, the other major factors considered when choosing one type over another include airborne concentration, outflow cleanliness, and cost. Air cleaners for removing gases and vapors normally either work on the principle of absorption, adsorption, condensation, or catalytic conversion. For metals fumes, a cloth filter, high efficiency wet collector, or electrostatic precipitator provides the best removal efficiencies. Particles (or dust) of sizes greater than 1 μm can usually be cleaned effectively by such control technologies as cyclones, precipitators, venture scrubbers, settling chambers, settling chambers, and cloth filters. Particles smaller than 1 μm are typically controlled with HEPA or ULPA filter setups. A considerable control challenge is presented by significant concentrations of particles, smoke, of fumes of less than one micron. These stressors show active Brownian movement because of their small size and do not tend to settle out like those particulate contaminants that are greater than 1 μm or so.

The required removal efficiency is an important parameter that needs to be covered on any discussion on air cleaners. Many operations in the device industry require robust collection efficiencies in order to keep the atmosphere at "clean" levels. For example, HEPA and ULPA filters are rated on their ability to remove a certain percentage of particles at a particular diameter. The efficiency and particle sizes specified vary from manufacturer to manufacturer, however, a typical claim for a HEPA filter may be something like '99.99 % removal efficiency of particles 0.3 μm and larger.' Likewise, for a ULPA filter it may claim a '99.997 % removal efficiency of particles greater than 0.1 μm.'

The fan is the mechanical driver of the LEV system and typically is of a centrifugal or axial configuration. The fan is rated based on the required volumetric airflow and static pressure. In addition, specifications for such parameters as voltage, current, revolutions per minute (rpm), outlet velocity, and brake horsepower (BHP) are typically made by the designer, and capacity tables are available from the fan manufacturer to assist in the decision making process. Important criteria that should be taken into consideration in the fan selection process include:

1. The characteristics of the airstream such as contaminant identity and physical state.
2. An evaluation of the physical constraints within its environment.
3. An analysis of the proper drive arrangement and potential configuration.
4. A prediction of the additional noise to be generated by the fan.
5. The dealing with any potential safety concerns posed by its use.
6. An assessment of the requirements for any supplemental accessories.

The exhaust stack is the final component of the complete LEV system, and is simply just an extension of the ventilation system's ductwork above the building rooftop. A properly designed stack will serve two important purposes. First, it should aid in the adequate dispersion of the gas stream stressors well above and beyond the roofline of the facility. Second, the mere existence of the stack in the LEV system causes a reduction in the velocity pressure at the outlet, and therefore, and an overall increase in fan performance. Some rule of thumbs that should be considered for optimal stack design include:

1. The stack should be configured as a straight cylinder to avoid any mechanical losses.
2. The use of rain caps or screens is not recommended.
3. If possible, the location of the stack should be on the highest rooftop.
4. The stack should be kept as far away as possible from any plant air intakes.
5. Stack height increases in lieu of good emission controls should be avoided.
6. Stack height requirements should be increased rather than gas stream exit velocities in order to realize the necessary control.

For those interested in more detailed information on how to design an effective and efficient LEV system for their specific process, a myriad of excellent resources are available for guidance through the design process.

## 10.17 Personal Protective Equipment and Clothing

A final control option for consideration in biomedical device manufacturing is the use of PPE or personal protective clothing (PPC). However, the paradox lies in the reality that the use of PPE or PPC is many times the easiest contaminant control solution. For example, the device manufacturer might use a dermal barrier device

(e.g., neoprene gloves, barrier cream, etc.) long before ever considering a change of process or materials. Other common examples of PPE and PPC usage in biomedical device manufacturing include ear plugs and muffs for noise protection, cooling vests for heat stress protection, and safety glasses for general eye protection.

The PPE and PPC usage in the industry varies widely and is based upon the type of device being manufactured. A detailed discussion on the various PPE and PPC usage in the various device manufacturing environments is beyond the scope of this chapter and will not be covered in any further detail.

## 10.18 Control Strategies in Device Manufacturing

The choice of the optimal control strategy to follow depends on a multitude of different factors. Obviously, the type of device being manufactured and the potential stressors associated with its production top this list. However, such additional factors as economics, regulatory requirements, workforce characteristics, and facility design must also be given due attention.

Typically, the best strategy involves the combination of two or more of the discussed control strategies. For example, a barrier or isolation control technique may be used in conjunction with an adequately designed LEV system in order to prevent environmental releases of worker exposures to ethylene oxide during the sterilization process. Another example might be the reliance on dilution ventilation to remove the majority of facility contaminants, with LEVs installed at questionable operations in enclosed areas. Table 10.6 provides the typical strategy (or strategies)

**Table 10.6** Control strategies in device manufacturing

| Category of stressor(s) | Control strategies |
|---|---|
| Ionizing radiation (Co-60 or various gamma and beta sources) | Time, distance, shielding, PPE, LEV |
| Organic degreasing solvents (TCE, 1,1,1-TCA, perchloroethylene) | LEV, dilution ventilation, substitution |
| Acid etching agents (e.g., sulfuric acid, phosphoric acid, chromic acid) | LEV, PPE |
| Particles or aerosols from various operations | HEPA or ULPA filtration |
| Microbial stressors from indoor air quality issues | Dilution ventilation with control over HVAC; HEPA or ULPA |
| Adhesives and coatings | Process control (i.e., continuous operations over batch), robotic application |
| Nonionizing radiation (e.g., lasers, microwaves) | PPE, enclosure/isolation |
| Welding and soldering contaminants (e.g., metal fumes, flux, ozone) | LEV, substitution |
| Toxic gases and vapors (e.g., EtO, methanol) | Isolation/enclosure, LEV, substitution |

**Table 10.7** Comparison of clean room international standards

| International Standard Organization | Germany VDI 2083 | USA 209D | Britain BS 5295 | Australia AS 1386 | France AFNOR NFX 44-101 |
|---|---|---|---|---|---|
| 3 | 1 | 1 | C | 0.035 | – |
| 4 | 2 | 10 | D | 0.35 | – |
| 5 | 3 | 100 | E or F | 3.5 | 4000 |
| 6 | 4 | 1000 | G or H | 35 | – |
| 7 | 5 | 10000 | J | 350 | 400000 |
| 8 | 6 | 100000 | K | 3500 | 4000000 |

followed to control some of the more common stressors found in the biomedical device manufacturing environment.

Control of the clean room environment in biomedical device manufacturing has been realized primarily through the standardization of equipment, facilities, and operational methods. These methods include procedural limits, operational limits, and testing procedures aimed at achieving internationally the desired environmental attributes to minimize microscale contamination. Clean rooms can have localized and enclosed forms of ventilation and contaminant removal or robust area HVAC systems capable of minimizing particle and microbial contamination. A comparison of the current international standards for classifications of clean rooms is given in Table 10.7.

## 10.19 Monitoring

The use of instruments and techniques to monitor for various hazards common to the device industry is an essential and complementary part of the overall exposure control process. While environmental monitoring will be conducted for various specific reasons, the real impetus behind this activity is to determine the extent of the facility contamination that exists in relationship to the worker and environment. The way that it is performed will normally depend on the actual (or perceived) stressors that are present as well as the existence of any outside pressures, such as regulatory compliance. The overall goal of an effective monitoring program, of course, is to keep the biomedical device employee and the environment free from the potential adverse health impacts from exposures to associated stressors.

While several authors have attempted to segregate or classify the various monitoring techniques and instrumentation in different ways, the simplest strategy for this discussion might be to just break these down into categories by environmental media (i.e., air, water, soil, artifact) and exposure target (i.e., personal or area). For example, if one wants to know the extent of the contamination of a groundwater source from a spill of a tanker filled with chlorinated hydrocarbons, several monitoring wells could be installed with the necessary sensors for

measuring these contaminants in real time. This would be classified as an area (target) monitoring event for groundwater (media) contaminants. Since the scope of this chapter is on the engineering control and monitoring of stressors in the biomedical device manufacturing industry, the majority of the techniques and instruments covered will be for personal exposures to primarily airborne stressors.

Airborne chemical, physical, and biological stressors can be classified as primarily either particles, fumes, vapors, gases, or electromagnetic radiation, with the techniques or instrumentation used dependent upon the particular category. Additionally, monitors for sound pressure energy and heat stress merit adequate coverage due to their potential importance in the industry. The following sections provide an overview of the techniques and instrumentation commonly used in the device industry to monitor for environmental stressors.

## 10.20 Particle, Fumes, and Aerosol Monitoring

The generation of significant concentrations of particles and dust will occur anywhere there is human activity; obviously, the biomedical device industry is not immune. With such particle-producing activities required in medical device production as surface preparations and coatings, light machining, and welding/soldering, the appropriate particle control and monitoring efforts must be implemented and followed in order to protect employees from the potential harmful effects associated with airborne exposures.

Some of the more commonly used techniques for area particle monitoring involve the use of either laser optics or condensation nuclei counting. In contrast, the current best practice in measuring employee exposures to airborne particulate concentrations is to use a personal sampling device to collect a representative volume of potentially contaminated air, typically conducted over an eight-hour workshift. The monitoring is conducted in compliance to approved analytical methods, with subsequent shipment of the completed samples on to an accredited laboratory for analysis. The metric most often used to determine a relative exposure to microscale particles is the time-weighted mass concentration of each particular aerosol. Table 10.8 provides a summary of particle measurement techniques that are either currently in the developmental stages or have already been implemented in the workplace. This table includes the method, the metric measured, the sensitivity, and the major capabilities and limitations of each.

The first method discussed is a personal sampling device that is size selective. Currently, most analytical methods for particulate matter are based on the collection on a pre-weighed filter of any additional mass sampled at a known airflow rate. This is typically weighed on a laboratory balance and the full production shift (i.e., 8 h) detection limit is approximately 0.02 mg/m$^3$. Obviously, the use of this technique would present a problem in analysis if the air sample comprised mainly of just particles in the nanoscale range, weighing normally only a fraction of this amount. However, with all of this said, it has still been suggested that a size-selective

**Table 10.8** Summary of particle measurement techniques

| Method or instrument | Measurement metric | Sensitivity ($10^{-9}$ m) | Major capabilities and limitations |
|---|---|---|---|
| Personal Sampler with accessories (e.g., cyclone, impactor, etc.) | Mass | 0.02 mg/m$^3$ | Acceptable for exposure compliance; no size fraction cutoff in nm size |
| Laser particle Counter and other optics counters | Number concentration | 300 | Portable and easy to operate; mainly for microscale use |
| Condensation particle counter (CPC) | Number concentration | 10 | Portable and easy to operate; not size selective |
| Scanning mobility particle sizer (SMPS) | Number concentration | 3 | Excellent sensitivity; not portable or user friendly and cost |
| Nanometer aerosol size analyzer | Number concentration | 3 | Excellent sensitivity; not portable and in development stage |
| MiPac particulate classifier | Number concentration | 10 | Ease of use; no detection under 10 nm |
| Electrical low pressure impactor (ELPI) | Number concentration | 7 | Successful use studies; cost and not portable |
| Epiphaniometer | Surface area | NA (surface area) | Successful use studies; bulky, complex, and costly |
| Gas adsorption | Surface area | NA (surface area) | Well understood technology; large samples sizes needed for validity |
| Scanning electron microscopy (SEM) | Number, size, and morphology | 5 | Excellent sensitivity and resolution; sophisticated instrumentation |
| Transmission electron microscopy (TEM) | Number, size, and morphology | 1 | Excellent sensitivity and resolution; complicated sampling routine |
| Laser induced plasma system | Composition | 3 | Outstanding for composition studies; composition information only |

personal sampler could be developed with, for instance, a 100 nm cut-off point. This could provide some meaningful accuracy for measuring any coating- or surface preparation-originating aerosols above approximately 50 nm in diameter. Figure 10.7 provides an example of the type of personal air sampler that would be used to monitor for respirable dust. Note that a cyclone is attached in order to collect the respirable fraction of the mass.

The second through seventh methods provided in Table 10.8 are based on the number of particles counted. These methods include laser optical particle counter, condensation nuclei counters, scanning mobility particle sizers (SMPSs), and electrical low pressure impactors. These are primarily real-time counters and range in relative portability, and subsequent applicability, to workplace exposure assessments. Also, several of these methods are still in the developmental stages.

**Fig. 10.7** Personal sampler used to monitor for respirable dust (*Permission* SKC, Inc.)

Due to its portability, versatility, and lower detection size limit, laser particle counters have been traditionally used to measure particles down in the low microscale range. However, particles that are less than 300 nm will not be detected by this method. This limits the applicability in the biomedical device manufacturing industry, in particular, the clean room environment, where particles of concern are quite frequently found at an order magnitude smaller. There are more sophisticated optical samplers but these are not currently portable devices, and therefore, would not typically be used in this industry to measure workplace exposures.

The most commonly used instrument capable of measuring ultrafine particles employs condensation particle counting technology. The condensation particle counter (CPC) condenses vapor onto the sampled particles in order to "grow" them to a detectable size range. This type of instrument is usually very portable and easy to operate. The main disadvantage to using this type of instrument is that it is not size selective and only provides the total particle counts above the detection limit, which ranges from 3 to 100 nm on commercially available units. Figure 10.8 shows an example of a typical CPC used to characterize ultrafine particles.

The measurement methods that are currently available, which provide both size-selective information as well as number concentration, are inherently more complicated to use as well as not being very portable or versatile for field exposure assessments. In addition, their higher costs typically eliminate applicability altogether in the workplace. The best instrument examples of these methods are the SMPS and the electrical low pressure impactor (ELPI). Both of these instruments can provide size-selective concentration data of particles all the way down to less than 10 nm in diameter. Examples of both an ELPI and an SMPS are provided in Figs. 10.9 and 10.10.


**Fig. 10.8** Condensation particle counter (*Permission* TSI, Inc.)

**Fig. 10.9** Electrical low pressure impactor (*Permission* Dekati, Ltd.)

While microscale particles typically do not agglomerate significantly, the majority of nanoscale-sized particles generated do agglomerate to some extent. Therefore, it can be argued that the best way to characterize nanoscale particles is by the measurement of its surface area. The only instrument that has been currently employed to measure surface area is called an epiphaniometer. This instrument uses radioactive tagging to determine the particle's surface area. Again, this instrument


**Fig. 10.10** Scanning mobility particle sizer (*Permission* TSI, Inc.)

is very complicated and lacks versatility for field use. Gas adsorption techniques that require rather large sample sizes have also been used infrequently as a bulk method of ascertaining particle surface areas.

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) also provide the means for determining particle and dust characteristics. While these instruments provide the morphology of the particles and excellent resolutions (e.g., TEM = 1 nm; SEM = 5 nm), they are very expensive and usually require an expert technician or specialized training to use effectively. However, recent studies point to the merit of this technique to characterize exposures in the workplace.

Micro- and nanoparticle composition measurements are normally essential components for detailed particle research studies. Not unlike many of the number, size-selective, and surface area techniques previously discussed, most composition techniques are currently in the developmental stages. The laser-induced plasma system and the high temperature nanoparticle measurement systems can detect the composition of nanoscale particles as small as 3 nm.

Each of the portable methods for area monitoring that have been discussed has their own set of merits and limitations. In order to alleviate the negative impact posed by some of these specific limitations, the use of two or more of these techniques in combination may be considered. While the more sophisticated instruments have excellent resolution and many times both concentration and size-selectability, they are primarily limited to research settings due to their complexity, size, and costs. And, for the majority of end users, personal exposure sampling devices, like the one shown in Fig. 10.7, coupled with one clean room portable particle measuring device, will be more than adequate.

## 10.21 Vapors and Gases

Techniques for monitoring the air for gases and vapors are essentially the same, thus, including them together in a section is appropriate. Both active and passive sampling methods exist to measure concentrations of many of the typical stressors found in device manufacturing such as ethylene oxide, trichloroethylene, phosphoric acid, and isopropanol (IPA). In order to conduct personal exposure monitoring for gases and vapors, an active sampling train such as the one shown in Fig. 10.11 should be used. Once this sampling train is calibrated to a known volumetric flow rate, it can be attached to the worker in order to monitor breathing zone air or placed at a site of concern to conduct an area monitoring event. In each case, the active setup will include a sampling pump, a calibrator, flexible hose, connectors, and some form of sampling media. The sampling media typically will capture the gas or vapor through sorbent action (e.g., adsorption, absorption). Depending on the compliance standard and protocol, a worker will normally be evaluated for his/her exposure for the whole workshift. Like particle exposure monitoring, once the sampling event is completed to accepted protocol, the filter is sent off to an accredited lab for quantification. Normal media material for monitoring airborne contaminants includes activated charcoal, silica gel, or a series of organic polymers.

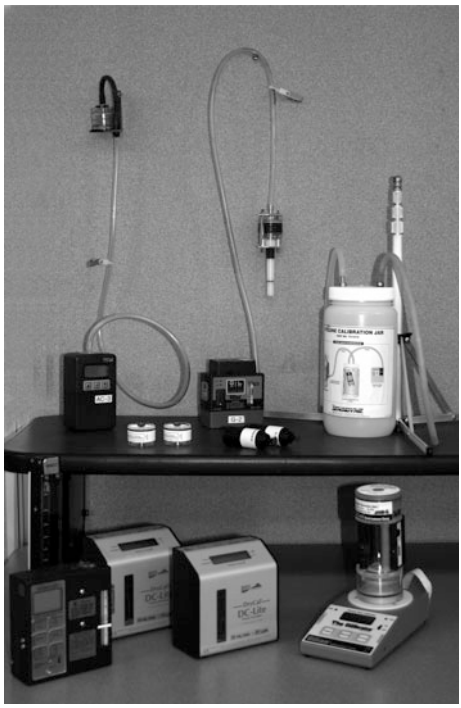

**Fig. 10.11** Personal exposure air sampling equipment

There are now also passive methods for monitoring workplace and environmental exposures to some gases and vapors. For example, ethylene oxide, the common sterilizer, has a fully validated passive method of monitoring. The passive monitors are typically worn as badges or dosimeters. After the monitoring event duration is complete and in similar fashion to both loaded filters and absorbent media samples, the dosimeter or badge is packaged up and sent off to an accredited lab for subsequent analysis. While lab quantification is still the usual means of analysis for compliance testing, there is a current impetus to test and approve direct-reading techniques for monitoring workplace exposures. Before a company considers conducting a comprehensive personal exposure assessment, it is recommended that an evaluation using direct-reading instruments and/or colorimetric techniques be performed to screen the potentially contaminated areas and develop a concentration profile of the facility.

There are several techniques for conducting this "snapshot" monitoring scheme, with normally a significant payoff realized by the company due to the useful information obtained. These instruments work on such principles as X-ray fluorescence, ionization potential, and chemical luminescence. These techniques vary on their relative accuracies and resolution and either provide qualitative, quantitative, or both qualitative and quantitative data to the end user. Due to their significance and usefulness, the following paragraphs elucidate the principles and operational characteristics of these instruments and techniques with respect to the common gases and vapors found in biomedical device manufacturing.

### *10.21.1 Detector (Colorimetric) Tubes*

The use of detector tubes to provide a concentration profile in the workplace is common due primarily to economics. These tubes are available for a wide variety of organic and inorganic vapors as well as for common gases found in industry and in the environmental field. A monitoring event can be conducted with one or even several colorimetric tubes for a fraction of the cost of some of the available survey instruments calibrated to measure the same stressor. Typically, ten tubes are included in a package with easy instructions on how to use them effectively in the field. The principle of operation involves a colorimetric reaction between the sorbent material in the tubes and the gas or vapor being monitored. While this technique is an excellent means of determining whether or not a contaminant exists in appreciable concentrations, it cannot be used for compliance purposes for employee exposures. The tube has other colorimetric chemical interferences and a normal concentration accuracy of only about 60–70 %. However, this technique provides an inexpensive means for detecting several common airborne contaminants in the biomedical industry. Colorimetric tubes are considered to be both a qualitative and pseudoquantitative in nature. The list of contaminants identified and partially quantified includes methanol, isopropanol, ethanol, trichloroethylene, methyl chloroform, perchloroethylene, sulfuric acid, and phosphoric acid, to name a few.

For those just getting into the characterization phase of the worker exposure assessment program, the use of colorimetric tubes make the most sense initially. Additional instrumentation can be acquired subsequently, if needed, as the level of survey and assessment procedure becomes more sophisticated. Figure 10.12 provides an example of a detector tube used to measure methanol concentrations. Figure 10.13 (top, right) shows the latest generation of colorimetric detection device.

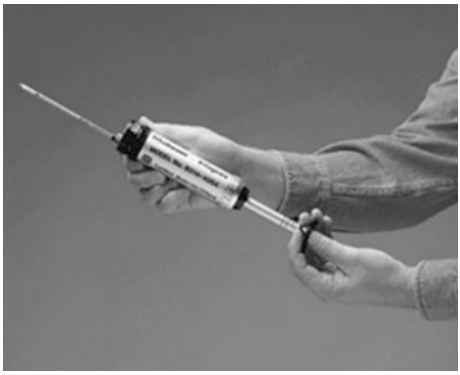

**Fig. 10.12** Colorimetric tubes for field surveys (*Permission* TerraUniversal)


**Fig. 10.13** Examples of field portable air monitoring instrumentation

### 10.21.2 Photoionization Detectors (PIDs)

The photoionization detector, or PID, is another common means for detecting organic vapors and gases in the workplace. The PID works on the principle that vapors and gases will ionize if a sufficient source of energy (e.g., UV radiation from a lamp) is allowed to come into intimate contact with them in a chamber. The PIDs have a range of ionization energy potentials, with 9.5, 10.2, and 11.7 eV being the most common. The different energies are a means for differentiating between two or more contaminants coexisting in a particular airspace. However, the instrument does not have the ability to determine the different contaminants by any direct means. Thus, it is considered to be quantitative but not qualitative in nature. The ionization potential of common device industry stressors include the values of 10.56 eV for EtO, 10.10 eV for IPA, and 9.45 eV for TCE [25]. An example of a common PID is given in Fig. 10.13 (top, left).

The biomedical device manufacturing professional might use this instrument if a known chemical hazard is possibly present at unsafe levels. As long as there are no other significant concentrations of different gases or vapors, which ionize at or under the ionization energy output of the device, a calibrated device should provide an accurate (e.g., within ±2 ppm or 10 % of the reading) representation of the concentration existing at any point in time. Of course, this assumes that the known gas being evaluated ionizes at or under the lamps ionization energy. The normal resolution of a commercially available PID is 0.1 ppm. Common industry contaminants that can be characterized by a PID include the various sterilizers, cleaning solvents, coatings, and adhesives.

### 10.21.3 Flame Ionization Detectors (FIDs)

The flame ionization detector, or FID, is another means for detecting primarily organic vapors and also works on the principle of ionization potential. However, in contrast to the PID, the FID energy source is a hydrogen gas-initiated flame. Because of the hot flame, this instrument is capable of a wider range of ionization potentials. For this reason, it is used many times in conjunction with a PID out in the environmental field where substantial concentrations of methane gas, with an ionization potential of 12.98 eV, may exist. Essentially, the two instruments are used in conjunction to identify both the methane concentration of the air as well as the concentration of organic vapors that exist. In essence, the trained user can differentiate the concentrations by subtracting the PID concentration (i.e., parts per million of organic vapors other than methane only) concentration from the FID output (i.e., parts per million of both organic vapors and methane) to get the total methane. Due to its use of an explosive gas as the energy source and complicated operational characteristics, this instrument is used mainly in the environmental field and would unlikely ever be considered for use in the biomedical device industry.

Figure 10.13 (bottom, right) shows an example of a flame ionization detector coupled with a gas chromatograph column. Figure 10.13 (top, middle) also shows a combination PID/FID instrument for field surveys.

### *10.21.4 Electrochemical Sensor Monitors*

Electrochemical sensor monitors are available from the original one gas monitor all the way up to the present day, five-sensor model. Typically, these monitors measure percent oxygen, percent lower explosive limit, hydrogen sulfide concentration, carbon monoxide concentration, and an end user gas concentration of choice. However, any of the sensors can be interchanged and the programming functions allow for customizing to the application. A common electrochemical multigas monitor to be used in the biomedical device industry might include sensors for ethylene oxide, % oxygen, hydrogen peroxide, ozone, and carbon monoxide. This device is considered to be both qualitative and quantitative, with accuracies of approximately ±5 % and resolutions of 0.1 ppm. Figure 10.13 (bottom, left) provides an example of a multigas monitor.

### *10.21.5 Infrared Spectrophotometers*

Portable infrared spectrophotometers are also available to measure airborne organic and inorganic contaminants. These are sensitive instruments with a series of mirrors that direct significant wavelengths within the unit. These are bulkier instruments that cost several times the amount of a PID, and thus, are currently in limited use in the biomedical device industry. However, this may change in the near future due to decreases in size and pricing, coupled with the instrument's inherent capability of providing relatively accurate qualitative and quantitative concentration measurements for many of the common airborne contaminants found in the industry.

### *10.21.6 Gas Chromatographs (GCs)*

While gas chromatographs (GCs) have been used for years as lab bench top instruments to identify and quantify many organic compounds, the technology has only been portable for the last couple of decades. Like the infrared spectrophotometers, the inherent cost and complexity of operating these units have limited their usage in the field. Still, with only a few known contaminants and an experienced operator, this instrument provides a viable option to monitor many of the airborne contaminants found in the device industry. Figure 10.13 (bottom, right) provides an example of a commercially available GC unit, couple with a FID.

**Fig. 10.14** Portable XRF being used in the field to characterize heavy metals (*Permission* Niton)

### *10.21.7 X-ray Fluorescence (XRFs)*

Portable X-ray fluorescence instruments provide an alternative for measuring heavy metals in the environment. The units are very portable and use a radioactive gamma-emitting source to produce the characteristic X-rays for each heavy metal of concern. While being relatively costly, they have the added benefit of being approved for usage on an airborne lead compliance method, with additional methods targeting the measurement of other heavy metals currently in the validation stage. This unit would be used to monitor concentrations of heavy metals during such operations as welding or machining. An example of a typical portable XRF is provided in Fig. 10.14.

## 10.22 Ionizing Radiation

The main types of ionizing radiation found in the biomedical device industry include gamma ray, X-ray, beta particle, alpha particle, and electron beam. The worker's occupational exposure to the various forms of ionizing radiation is typically monitored by the use of personal dosimeters and portable survey meters. Some of the most common operations for sterilizing medical devices employ the use of radioactive sources. In addition, radioactive tracers are many times used during the research phase of the device development, with sources also included as integral components in some the lab instrumentation.

Worker exposure could be monitored during the workshift by personal dosimeters, such as a thermoluminescent dosimeter (TLD). This is simply worn for the time period and then removed and analyzed by a qualified technician. Additionally, there are other active and passive dosimeters designed specifically to measure the dose of certain types of ionizing radiation to which an individual may be exposed. Another means for determining worker exposure is by performing a

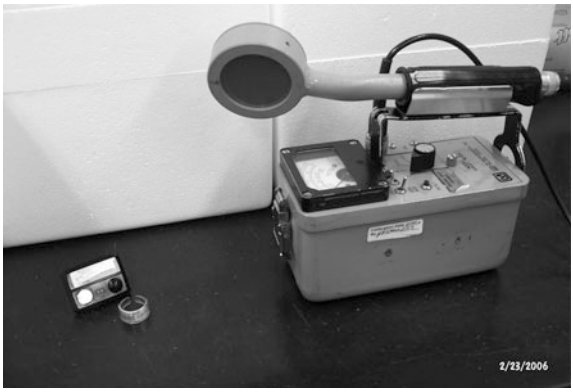


**Fig. 10.15** Radiation dosimeter (*left*) and Geiger-Mueller counter for radioactivity surveys

bioassay after the event. A detailed discussion on these various dosimeters and their appropriate uses is beyond the scope of this chapter.

As for the survey-type instruments, the type of detector will be chosen based on whether or not the source of radiation is gamma/X-ray, beta, alpha, or electron beam. Normally, a Geiger-Mueller survey meter will be the instrument of choice, with various added capabilities such as data logging and programmability. Both a common radiation dosimeter and a Geiger-Mueller counter, with associated detector, are shown in Fig. 10.15.

## 10.23 Nonionizing Radiation

The major forms of nonionizing radiation that a worker may be exposed to in this industry include, but are not limited to, laser, ultraviolet, microwave, and infrared. The majority of nonionizing radiation monitors provide an output on the magnitude of both the electric and magnetic fields associated with their operations. Other important parameters that must be ascertained include the frequency, wavelength, duration of both signal and exposure, and power of the source. These are determined by various instruments and techniques and are not outputs from just a single monitor. Figure 10.16 shows a monitor capable of measuring the associated fields produced by a particular nonionizing source.

## 10.24 Noise and Heat Stress

Personal exposures to noise are monitored by noise dosimeters. They are typically attached to the worker and allowed to collect the data for the entire workshift. The value is then integrated over the duration and then compared to the acceptable time-weighted average for the time frame. To determine area noise levels or

**Fig. 10.16** Monitor for measuring electromagnetic radiation (*Permission* Gentec-EO)

environmental noise, an instrument known as a sound level meter (SLM) is typically used to log the data. This instrument provides a means for determining a noise profile for a whole facility. Once the problem areas are identified, personal exposure monitoring is conducted for those potentially overexposed. Figure 10.17 provides examples of both typical noise dosimeters (middle) as well as a common type of SLM (right).

Heat stress monitoring is normally conducted using a wet bulb globe temperature apparatus. This instrument provides a combination measure of the effects of dry air temperature, radiant heat transfer, and humidity. While there is no universal standard for heat stress, there are guidelines that normally involve work–rest regimens and different work rates. While the use of this monitor in the biomedical device manufacturing environment would be atypical, there still could be conditions necessitating its use (e.g., laborious maintenance activities). A portable heat stress monitor is also shown in Fig. 10.17 (left).

## 10.25 Microbial Environmental Monitoring

Significant concentrations of contaminants originating from biological origin are often found in the device industry. In particular, there is a major concern to limit the amount of microbial activity in the facility air (and on surfaces) due to the nature of


**Fig. 10.17** Monitors for heat stress (*left*), noise dosimetry (*center*), and sound level measurement (*Permission* Quest Technologies, Inc.)

the product. Biomedical device manufacturers use microbial environmental monitoring programs to evaluate the effectiveness of facility-wide cleaning and disinfection procedures as well as to assess the overall microbial cleanliness of their manufacturing environment. The ultimate goal must be to minimize the bioburden on the biomedical device being manufactured. If allowed to exist, undesirable bioburden spikes on the finished product can cause a reduction in the sterility assurance level for the device.

**Fig. 10.18** Viable contaminant monitoring apparatus with agar plates

In order to manage and control the indoor environment with respect to biological stressors, usually it is necessary to get a baseline of contamination through an approved microbial environmental monitoring procedure. This procedure normally includes a sampling train made up of a calibrator, vacuum pump, Anderson impactor (or comparable), and necessary tubing and accessories. The sample media is usually an agar plate prepared with the proper substrate of microbial subsistence. Figure 10.18 gives an example of a typical biological stressor monitoring apparatus.

The available monitors, like the one shown in Fig. 10.18, typically work on the principle of collecting a known volume of air at a certain flow rate and then, in much the same fashion as for chemical samples, the sampling media is shipped off to an accredited lab for subsequent analysis. The monitoring duration varies based on the collection procedure and objective for monitoring, but typically is less than 20 min per location. Since personal exposure standards are essentially nonexistent at this time from most biological contaminants, area monitoring is the only type currently conducted in the majority of cases.

## 10.26 Clean Room Monitoring Requirements

In the majority of biomedical device manufacturing settings, there will exist at least one condition or operation that requires a mandated clean room environment. Therefore, it is appropriate to discuss the monitoring requirements in order to meet compliance standards as a separate topic altogether in this section. Current international regulations require the monitoring of particulate matter and biological agents as a part of good manufacturing practice. The following paragraphs provide an overview of details surrounding proper clean room monitoring.

Table 10.9 provides the airborne classification used by the EU as the guide to good manufacturing practice (EU 2003). Grade A and B correspond to a class 100 (USFDA) or ISO 5 clean room while Grade C corresponds to a class 10000 or ISO 7 clean room and a Grade D corresponds to a class 100000 or ISO 8 clean room. The particle monitoring requirements can either be completed manually or automatically, and typically measurements of the critical sizes (i.e., 0.5 and 5.0 μm) are taken with a laser-based detector with an isokinetic sampling probe. Normal flow rates and sampling duration at each monitoring location are 1.0 cubic feet per minute and 20 min, respectively; however, this rate and duration will vary on case-to-case basis. For clean rooms of ISO 5 and lower, the mandatory testing time interval to demonstrate compliance to particle limit standards is every 6 months, with those greater than ISO 5 required to be tested every 12 months. Air pressure differentials and airflow velocity is also required at 12-month intervals. Portable devices which measure both air velocity and pressure are commercially available and normally used to quantify these parameters. The number of monitoring locations per site varies based on class level and regulatory authority, respectively.

There are also limits to the microbial contamination that exists in a clean room environment. Thus, the monitoring of the clean room air for total microbes is essential to attain and maintain compliance. Figure 10.18 provides an excellent example of the monitoring setup typically used to collect the colony forming units (cpu) for each air sample. Additionally, there are cpu sampling requirements for settle plates, contact plates, and gloves. The EU GMP for recommended limits at each grade level for microbial contamination for all four of these is shown in Table 10.10.

**Table 10.9** Airborne particle classification in the EU guide to good manufacturing practice (maximum number of particles permitted per cubic meter)

| Grade | $\geq$0.5 μm (at rest) | $\geq$5.0 μm (at rest) | $\geq$0.5 μm (in operation) | $\geq$5.0 μm |
|---|---|---|---|---|
| A | 3500 | 0 | 3500 | 0 |
| B | 3500 | 0 | 350,000 | 2000 |
| C | 350,000 | 2000 | 3,500,000 | 20,000 |
| D | 3,500,000 | 20,000 | Not defined | Not defined |

**Table 10.10** Airborne microbial classification in the EU guide to good manufacturing practice

| Grade | Air sample cfu/$m^3$ | Settle plates 90 mm diameter cfu/$m^3$ | Contact plates 55 mm diameter cfu/$m^3$ | Glove print (5 fingers) cfu/glove |
|---|---|---|---|---|
| A | <1 | <1 | <1 | <1 |
| B | 10 | 5 | 5 | 5 |
| C | 100 | 50 | 25 | – |
| D | 200 | 100 | 50 | – |

## 10.27 Monitor Selection in Device Manufacturing

The choice of the best monitor for the application is based on such factors as the type and physical state of the stressor, environmental media contaminated, concentration of the contaminant, goal of the monitoring effort, and overall economics. If the monitoring event is just to provide an area characterization of the extent of contamination, many of the direct-reading instruments and techniques may suffice. However, if the goal is to show environmental or occupational regulatory compliance, then personal monitoring techniques, with subsequent accredited lab testing and analysis, is the correct choice. Table 10.11 pairs up some of the more common industry stressors with the instrument or technique normally used to

**Table 10.11** Common stressor and instruments/techniques normally used to characterize

| Chemical, physical, or biological stressor | Instrument or technique |
|---|---|
| Cleaning and disinfecting alcohols (e.g., methanol, isopropanol, ethanol, etc.) | PID, detector tubes (area or snapshot/screening)<br>Sampling pump with silica gel media (personal or area) |
| Chlorinated hydrocarbons for cleaning and degreasing (e.g., TCE, Perk, etc.) | PID, detector tubes (area or snapshot/screening)<br>Sampling pump with activated charcoal media (personal or area) |
| Ethylene oxide from sterilization | Electrochemical sensors (area or snapshot/screening)<br>Sampling pump with activated charcoal media or passive badge (personal or area) |
| Ozone from sterilization, welding activities, and air cleaners | Electrochemical sensors, detectors tubes (area or snapshot/screening)<br>Sampling pump with coated glass filter media (personal or area) |
| Hydrogen peroxide from disinfecting and sterilization | Electrochemical sensors, detector tubes (area or snapshot/screening)<br>Sampling pump with impinger (personal or area) |
| Heavy metals from welding and machining operations | X-ray fluorescence (area, snapshot/screening, or personal)<br>Sampling pump with 0.8 μm mixed cellulose filter media (personal) |

(continued)

**Table 10.11** (continued)

| Chemical, physical, or biological stressor | Instrument or technique |
|---|---|
| Particulate matter and dust from a myriad of sources | Laser counters, condensation nuclei counters (area or snapshot/screening)<br>Sampling pump with cyclone and filter media (personal) |
| Acids and alkalis used for etching and anodizing | Detector tubes, IR spec (area or snapshot/screening)<br>Sampling pump with activated charcoal media (personal) |
| Gamma radiation from sterilization and instrument-specific sources | Geiger-Mueller survey meter with gamma detector (area and survey)<br>TLD, film badge, or other dosimeter (personal) |
| Fungal and bacterial species from indoor air quality problems | Impactor with high volume sampling pump and agar plate (area and survey) |
| Noise from plant and maintenance activities | Sound level meter (area and survey)<br>Dosimeter (personal) |

identify and/or quantify each. The second column of Table 10.11 also identifies whether or not the instrument or technique is typically used for area, snapshot/screening, or personal monitoring events.

## 10.28 Summary

The effective monitoring and control of chemical, biological, and physical stressors in the biomedical device manufacturing environment is imperative. This chapter began with an overview of the sources, properties, and characteristics of some of the more common contaminants found in the industry. Once these stressors were identified and characterized, examples of some of the more typical techniques implemented for controlling their presence in the workplace and the potential risk of exposures associated with each were discussed. The chapter concluded with a synopsis of the potential monitoring techniques and instruments that may be used as a means to qualify and quantify the extent of contamination and potential employee exposures to the hazardous stressors inherent to biomedical device manufacturing.

**Acknowledgments** The authors thank Springer and Wiley publishers for allowing the authors permission to reprint and update this chapter that was originally published in, 'Surface Engineered Surgical Tools and Medical Devices,' originally published by Springer in 2007 (ISBN 978-0387-27026-5). *Reprinted with kind permission from Springer Science+Business Media B.V and Wiley Publishers.*

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