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About the Cover

When studying highly virulent animal pathogens special containment practices and facilities are required, ranging from BSL-3 enhanced to Biosafety Level 3 Agriculture (BSL-3-Ag). As the recent outbreak of foot and mouth disease in England shows, high containment practices, facilities and facility maintenance are vital to working safely with these pathogens in the laboratory and vivarium. The pictures show a mock drawing of a BSL-3-Ag facility and its relationship of support space versus animal space (courtesy of Merrick and Company as drawn for the USDA Ames modernization project), turkeys ready for study, an air pressure resistant door, and sheep within BSL-3-Ag containment (courtesy of USDA ARS National Animal Disease Center). For more information on this topic, please see the article entitled “Biosafety Levels for Animal Agriculture Pathogens” by R. A. Heckert et al. on pages 168-174.
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- April 20 for Summer issue
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- October 15 for Winter issue

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Vision

ABSA, the leader in the profession of biological safety.

Mission Statement

The American Biological Safety Association is dedicated to expanding biological safety awareness to prevent adverse occupational and environmental impact from biohazards.

Goals

- Expand professional and public awareness of biological safety through effective communication.
- Participate in the development of biological safety and biosecurity standards, guidelines, and regulations.
- Develop ABSA as the recognized resource for professional and scientific expertise in biological safety and biosecurity.
- Advance biological safety as a scientific discipline through education, research, and professional development.

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In a few days we will meet in Nashville, Tennessee for our 50th Annual Biological Safety Conference. Dan Liberman and his Scientific Program Committee Team, and LouAnn Burnett and her Local Arrangements Committee Team have assembled an educational and entertaining program. The schedule of events may be modified this year in order to accommodate all of the activities, while still maintaining a Sunday through Wednesday conference. This is a result of our steady growth (membership is currently at 1,435) and the fantastic interest expressed by many individuals wishing to present their studies! Many of our colleagues from overseas will be attending the conference. Specifically, we anticipate a large delegation of more than 100 people from the Former Soviet Union, Asia, and the Middle East. Many of them will be attending some pre-conference courses, assisted with simultaneous translations. The 28 scheduled pre-conference courses have been organized by Patrick and Michelle McKinney. Their Educational Operations Committee Team will hopefully satisfy the “thirst for knowledge” of all participants. As during previous conferences, I ask you to please complete the evaluation forms for both the pre-conference courses and the conference program as your comments will help guide our organization for future events.

There are several other points of interest that I would like to mention: The Chesapeake Affiliate of the American Biological Safety Association (ChABSA) held its Annual Scientific Symposium on June 14 in Columbia, Maryland. Bruce Donato and his Scientific Program Committee Team organized a stimulating and educational one-day program. The Keynote Speaker was Dr. David Franz of Midwest Research Institute; Kansas State University, University of Alabama at Birmingham, who gave a presentation entitled Biological Safety: A Tool of International Diplomacy? Representing ABSA, I gave a presentation entitled ABSA—State of Your Organization. ChABSA was well-funded through various sponsors and vendors providing various products and services for the biological safety community.

The Alliance with the Federal Bureau of Investigation (FBI), led by Jim Klenner and Jeff Owens, will be formalized sometime during July and August in Washington, DC. The purpose of this alliance is to establish mutually beneficial relationships with organizations, associations, and agencies. These relationships can assist the American Biological Safety Association (ABSA) in promoting biological safety (biosafety) as a scientific discipline and serving the needs of biosafety professionals throughout the world.

Of interest to many ABSA members is the recertification process for the designations Certified Biological Safety Professional (ABSA) and Specialist Microbiologist from the National Registry of Microbiologists (NRM). In order to streamline this process, the ABSA Office has submitted an application to the International Association for Continuing Education and Training (IACET) to receive continuing education unit (CEU) credit for pre-conference courses. We anticipate approval for the 2007 pre-conference courses. For all future pre-conference and other courses, the ABSA Office will complete the necessary documents for approval by IACET. The National Registry of Microbiologists (NRM) has a voluntary recertification program. Registrants have five years to earn the required 60 hours of continuing education (CE) credits to recertify and to maintain their active NRM status. Registrants must acquire 25 category 1 CE credits of the required 60 hours during the 5-year period. As a service to the Registrants, the NRM will review CE activities and evaluate if they are eligible for category 1 credits for NRM recertification purposes only. Obtaining course credit for NRM recertification is a relatively simple process. ABSA members can use the CE Point Request Form to obtain points for ABSA courses completed in the past. CE points will be awarded if activity has significant microbiology content, and is directly relevant to the practice of microbiology. A 0.5 CE will be awarded for each hour of educational activity, with each activity capping at 5.0 CE. These CE points are acceptable for Category 1 credits for NRM recertification only. They are not acceptable for NRM examination eligibility. The recertification form can be accessed at www.asm.org/ASM/files/ccLibraryFiles/FIELD/000000001595/NRM%20recertification%20form.doc. Please contact Kimberley Ver Ploeg, NRM Certification Program Assistant, at kverploeg@asmusa.org for a copy of the CE Point Request Form.

As I mentioned in my previous column, Council Member Dr. Robert Ellis, Colorado State University (CSU), will offer a two-year graduate program in biological safety at CSU beginning January 2008. Upon successful completion of the requirements, participants will re-
ceive a Master of Science in Microbiology with a concentration in biological safety. There is a requirement for residency, biological safety courses, a practicum (designed to give students supervised practical application of a previously studied theory), and completion of a thesis. The 2007 Biosafety and Biosecurity Training course session was completed during July 6-13, 2007 and addressed general, animal and plant issues related to biosafety. Registration information can be viewed at: www.cvmbs.colostate.edu/microbiology/crwad/relatedmeetings.htm. If you’re interested in this program, please contact Bob at Robert.Ellis@ColoState.EDU for current and additional information.

ABSA seeks your support, and I continuously seek your comments and suggestions that will be brought to the attention of your Council. Please let me know if you have any issues to be addressed, or if you wish to be involved with any committees or programs.

BMBL Comments from the ABSA Technical and Regulatory Review Committee

The ABSA Technical and Regulatory Review Committee has conducted a comprehensive review of the online version of the 5th Edition of the Biosafety in Microbiological and Biomedical Laboratories (BMBL). To read the full report of the comments provided to the 5th Edition BMBL Steering Committee, please visit www.absa.org/resrevcom.html.
When I was asked to contribute this guest editorial, at the front of my mind was the fact that containment facilities are designed to provide safety and security for the work that is done inside the lab. At no time should safety or security be compromised to promote sustainability. However, I believe there are many steps that you can take when you design a containment facility to make it a more environmentally responsible facility to operate during its planned life, and that these ideas should be shared with a broader audience. As Paul Jeanette eloquently explains in a course we teach, the most common words in containment facility design are “it depends.” In other words, a single answer rarely covers all of the issues for all containment facilities. Be sure to examine the applicability of the information provided below for your specific project needs before you implement them.

Sustainable design deals with a broad spectrum of design issues that reduce the impact of a facility on the environment. The U.S. Green Building Council, which administers the LEED certification process for facilities, categorizes the issues in five ways: Sustainable Sites, Water Efficiency, Energy and Atmosphere, Materials and Resources, and Indoor Environmental Quality. I will address how each one might impact on containment facility design.

**Sustainable Sites**

Sustainable sites refer to site selection and design to minimize a facilities impact on the environment. As this is not specific to containment facilities, I will not try to address these issues here.

**Water Efficiency**

Efficient use and reuse of water can be important in laboratory facility design; however, it has limited application in containment facility design and operations. One can take advantage of the sustainable water design features of a normal building such as low flow fixtures and minimized irrigation of plant materials. When you get to the specific water uses in a containment facility, such as showers and handwashing sinks, the appropriate flow is important when you need it. One heavy user of water in a containment facility is the autoclave during the cool-down cycle. Chilled water coils can be substituted for this water cool-down system and can significantly reduce the water used by the autoclave. This has an added benefit when you have an effluent decontamination system of reducing one of the major loads on the system. This reduces chemical use if decontamination is by chemicals, and energy use if decontamination is by heat treatment.

Support areas outside containment can provide areas of sustainable design. For example, the condensate from air handling units can be collected and used as grey water for toilet flushing or irrigation.

**Energy and Atmosphere**

Laboratory facilities use a high level of energy and other non-renewable resources. Significant design responses for containment facilities can greatly reduce the impact of these facilities. This is the area where containment facility design can have the biggest impact on the environment. When you study the energy use in laboratories, the energy used by fans to move air into and out of the facility is often a major contributor to overall building energy use. Fan horsepower, which is the energy it takes to move the air, can greatly be reduced by a good HVAC system design involving two factors: 1) reducing the static pressure loss in the system; and 2) reducing the quantity of air exhausted (and supplied).

Designing to minimize pressure loss can play a large factor. You may want to consider providing a low pressure system by increasing duct sizes to reduce friction loss, and using HEPA filters with lower pressure drop for the same quantity of air. Small changes in pressure loss can result in big energy savings, as energy use increases by the square of the pressure in the system.

In containment facilities, the quantity of air exhausted is driven by three factors: air change rates, local ventilation requirements, and the internal heat load that needs to be overcome by outside air. Studies over the past 25 years have shown that air change rates are not effective at reducing biological contamination in laboratories. One study demonstrated that increasing air changes from 6 to 30 per hour had a minimal impact on potential aerosols in the room. It is becoming generally accepted that lower ranges of air changes per hour (e.g., six to eight) are acceptable in containment facilities. If you use higher air change rates, consider reducing the air changes when the
laboratories are unoccupied. This may represent a significant energy savings. Take care, however, that you do not create a system that is difficult to balance and maintain. For Biosafety Level 3 (BSL-3) facilities, particularly rodent facilities with containment caging, provide the air changes for animal welfare within the cage, not the room. This can reduce the amount of air exhausted by half.

Local ventilation requirements in a BSL-3 laboratory are driven by the selection of the biological safety cabinets (BSC). For energy savings, use recirculated BSCs if your risk assessment allows. If you are required to exhaust BSCs, make your selection based on need. Canopy connected A2 cabinets require 20-100% more exhaust than a hard connected A2 cabinet; however, Annex E of NSF49 states “No type A cabinet should ever be hard connected to an exhaust system.” B2 cabinets require 250-300% more air (at much higher static pressure) than an A2 cabinet. Moving from an 8-inch high sash opening to a 10-inch high sash opening can add another 25% exhaust requirement. Moving from a 4-foot cabinet to a 6-foot cabinet will increase the exhaust requirement by 50%. To sum it up, two 6-foot B2 BSCs in a small room may require over 120 air changes per hour to produce the exhaust required, up to 20 times a reasonable minimum. A type B1 cabinet with an 8-inch opening would have about 1/3 the exhaust flow requirement of a B2. BSC selection should be based on the real risk assessment of the facility and should be made carefully. This is also an area where environmentally responsible design can reduce the initial construction costs.

Containment labs can have greatly varying heat loads; from BSCs to mechanical freezers, the laboratory air conditioning has to overcome a lot of heat. Instead of using outside air to provide all of the cooling, consider using local supplemental cooling such as fan coils, chilled beams, and radiant ceilings. Some of this technology may be new to containment; you’ll want to carefully evaluate the advantages and disadvantages and look carefully at maintenance issues.

For overall energy savings, consider recovering the heat and cooling from the exhaust stream. Many technologies are available and most would be appropriate in biocontainment with little, or no carryover from one air stream to another.

Lastly, correct system operation plays an important part in energy savings. Containment laboratories are usually highly commissioned; this savings is usually gained as an integral part of the containment laboratory delivery process.

**Materials and Resources**

The category relates to recycled content, local availability and renewable materials. As the materials in containment facilities often have specific requirements for performance, there are limitations on the options available to you.

**Indoor Environmental Quality**

The last LEED category is impacted both positively and negatively by containment facility design. One hundred percent ventilation, generally low chemical use, and the primary containment of biological hazards, translate to very good indoor air quality in containment labs. However, the need for flooring and wall coatings to be highly resistant to disinfectant chemicals limits choices for these materials. Depending on the actual needs of the facility, coatings may have a higher content of volatile organic compounds than green design would dictate.

Other indoor environmental issues, such as daylighting and views, can be incorporated into containment facilities with appropriate design. This can make these facilities very pleasant places to work. Task lighting, which comes automatically with BSCs, can improve work effectiveness and lower the overall light levels required in the space reducing operating costs.

While the above information does not represent all of the sustainable design options in a containment facility, it does argue strongly that sensitivity to green design, while planning a containment facility, can reduce first costs, reduce operating costs, and contribute to a sustainable world without compromising safety. That makes it an option that is hard to resist.

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**Guest Editorial**

The new online submission site for *Applied Biosafety* is user-friendly and available at www.xcd.com/absa/article.cfm. If you have any questions, please contact the Production Editor, Karen Savage, at the ABSA Office at 1-866-425-1385 (toll free) or 847-949-1517 or via e-mail at karen@absa.org.
Abstract

The requirements of laboratory facilities differ dramatically from those of other buildings. As we expand our biocontainment needs to Biosafety Levels (BSL) -2, -3, and -4, a clear need exists for an air quality and thermal comfort initiative targeting these facilities. The thermal comfort of occupants in laboratories can be controlled by the choice of ventilation strategy. Added benefits are the realization of a significant energy savings and improved indoor air quality. This study employs an advanced numerical simulation and empirical validation to assess the performance of active chilled beams in a general laboratory layout having some equipment intensive areas. The study examines the removal effectiveness of gases and airborne particles in such a system. Chilled beam performance is also compared to a ceiling diffuser system with and without cooling panels. The results of this study show that chilled beams improve thermal comfort and can be operated at reduced Air Changes per Hour (ACH) while maintaining a comfortable environment in occupied zones expressed as the Predicted Percentage Dissatisfied (PPD). To obtain a similar level of thermal comfort, a higher ACH is required in a ceiling diffuser system with cooling panels and bench exhausts. The chilled beam system also improves the removal effectiveness of gases or airborne particles because of the inherent better mixing in the room compared with the use of ceiling diffusers. In the cases studied, chilled beams have an insignificant effect on the fume hood containment. As satisfactory thermal comfort and air quality was achieved at a lower flow rate when compared with an all-air ceiling diffuser system, a savings of around 22% is estimated in annual energy costs for cooling and ventilating a typical lab in the Washington, DC area. The methodology and results of this study may be applied to further research for other laboratory types, or climatic conditions than those proposed in this study.

Introduction

A large portion of the laboratory space cooling load is from heat producing research equipment located on benches. Moreover, many chemicals used in laboratories are harmful to occupants' health. Inhalation exposure is a common concern raised by laboratory occupants. The ventilation flow rate required to cool these laboratories and meet local exhaust requirements is usually high. Care needs to be taken in the design of the ventilation system, particularly in instances where a fume hood and/or biosafety cabinet is present. In particular, significant airflow across, or into the face of the fume hood, can dramatically affect the hood containment. A general laboratory uses more energy and water per square foot than the typical office building due to ventilation requirements and other health and safety concerns. Because the requirements of laboratory facilities differ so dramatically from those of other buildings, a clear need exists for an initiative that exclusively targets these facilities. This is especially important as we move to Biosafety Levels (BSL) -2, -3, and -4. The use of chilled beams is not intended to be applicable to all types of laboratories. For example, the use of chilled beams would not be appropriate for BSL-3 or BSL-4 laboratories where the accepted methodologies for control should not be compromised. Further, chilled beams should only be considered for BSL-2 laboratories after extensive consultation with experienced engineers who understand the nature of the work performed in the laboratory. The use of chilled beams should not override the contaminant controls that are appropriate for a containment laboratory, particularly with respect to the use of appropriate biosafety cabinets (BSC), or the handling of hazardous materials on workbenches. Although parts of this study were conducted in the presence of a fume hood rather than biosafety cabinets, the results should be generally applicable to Class I and II biosafety cabinets (BSC). Typical BSC types involve a laminar airflow regime, which serves to protect the scientist from particulates as well as the product in the cabinet. The strict applicability of results from the fume hood cases to BSC scenarios is dependent on the flow profile at the sash and the average face velocity, which should be similar in both scenarios. Developed in the 1980s, chilled beams are a relatively new technology (Virta et al., 1995; Barista, 2005). This type of room air-conditioning has spread rapidly in Europe where it is used to provide comfort cooling in both new and refurbished commercial and industrial...
non-laboratory buildings. Chilled beams are flexible, simple to install and maintain, and provide an energy efficient, cost-effective alternative to traditional cooling systems. Chilled beams have not yet been employed in a laboratory setting, but the technology is sufficiently appropriate for BSL-1 and some BSL-2 laboratories.

There are two basic types of chilled beams: active and passive (Building Services Research and Information Association, 2001). Passive beams, which provide only cooling, rely entirely on the natural convection process with chilled water coils and no air supply to the unit. Room air supply is typically provided via floor, or low wall registers similar to displacement ventilation. Active beams with chilled water coils and an air supply connection, offer an increased cooling capacity using a primary air supply to cause induced convection over the water coils. The primary airflow required for fresh air supply is discharged into a mixing zone via nozzles. The induced air is drawn from the room through a water coil. In the mixing section, the induced air is mixed with the primary air and the total discharged into the room via slots as shown in Figure 1. With active chilled beams, the air is cooled by means of cold water, and the supply airflow rate is dimensioned in a way that fulfills the requirement of good air quality. Chilled beams combine the airflow characteristics of ceiling diffusers with the energy benefits of load dissipation using water. Active chilled beams can provide cooling, heating, and ventilation.

In all-air systems, air is used to ventilate the buildings in order to maintain a high level of indoor air quality as well as to provide thermal comfort in the buildings. With chilled beams, the airflow rates of the system need only satisfy the indoor air quality requirements. A cooling capacity, ranging from 90 W/m² to 120 W/m² can be provided by using a water-cooled coil system. The room air temperature can be controlled by regulating the water flow rate of the cooling coil. This is because water cooling can be more energy-efficient than air-based systems (Mumma, 2001); it requires less parasitic energy (pump and fan energy) to remove heat from a space. Laboratories that are heavily equipped present the most ideal application of chilled beam technology, because they often require many more air changes per hour than is required by code just to offset the heat gain from the lab equipment. By cooling and recirculating the air of the chilled beams, the amount of air changes in a typical lab can be reduced. With fewer air changes needed, ductwork, air-handling units, exhaust fans and chillers can all be downsized to offset the cost of the chilled beam units and infrastructure.

The use of radiant cooling panels or a chilled beam system is an alternative to air/water systems that separate the tasks of ventilation and thermal space conditioning by using the forced air to fulfill ventilation requirements and using radiant cooling panels to provide most of the cooling. In situations where the walls are radiantly cooled, the air temperature can be warmer to achieve the same level of comfort. A warmer air temperature results in lower energy loss to the outdoors. However, the preferred installation of the radiant cooling panel is ceiling mounted as this reduces air stratification and facilitates collection of condensation. This study also assesses the performances and energy costs of the cooling panel system and compares them with those of chilled beams.

**Purpose of This Study**

Focusing on active chilled beams, this study investigates and compares different types of ventilation strategies in their performances and annual energy costs. The primary objectives of this study are:

- To assess the performance of active chilled beams in achieving required thermal comfort with minimum ventilation flow rate requirements and compare it with that of a ceiling diffuser system with and without radiant cooling panels.
- To evaluate chilled beams’ effectiveness when it comes to removal of gases and airborne particles and

![Figure 1](Sketch of active chilled beams.)
their effects on fume hood containment.

• To evaluate the cost reduction as a result of using chilled beams with reduced ventilation flow rate.

Methodology and Validation

Computational Fluid Dynamics (CFD) is a very powerful and efficient methodology to study temperature and flow fielding in a room where there are many parameters involved (Memarzadeh, 1998; Jiang et al., 1995; Kang et al., 2001). It solves the set of Navier Stokes equations by superimposing a grid system containing a huge number of cells, which describe the physical geometry heat and contamination sources and air itself. Figure 2 shows a typical laboratory with space discretization subdividing the laboratory into the cells.

In this study, CFD with a finite-volume approach (Flomerics, 1995) was used to consider the discretization and solution of the equations. The simultaneous equations thus formed are solved iteratively for each one of these cells to produce a solution that satisfies the conservation laws for mass momentum and energy. As a result, the flow can then be traced in any part of the room simultaneously coloring the air according to another parameter such as temperature. The airflow in a ventilated laboratory is turbulent. In this study, the turbulence is simulated with the $k-\varepsilon$ model (Wilcox, 1993; Chen, 1995). The $k-\varepsilon$ turbulence model represents the most appropriate choice, because of its extensive use in other research applications such as predicting mixing rate of a jet flow and modeling airflow in urban open space (Gregory-Smith et al., 1996; Palmer et al., 2003). No other turbulence model has been developed that is as universally accepted as the $k-\varepsilon$ turbulence model.

This methodology was used extensively by Memarzadeh (Memarzadeh, 1998) in the “Ventilation Design Handbook on Animal Research Facilities Using Static Microisolators.” In order to analyze the ventilation performance of different settings, numerical methods based on CFD were used to create computer simulations of more than 160 different room configurations. The performance of this approach was successfully verified by comparison with an extensive set of experimental measurements. A total of 12.9 million experimental data values were collected to confirm the methodology. The average error between the experimental and computational values was 14.36% for temperature and velocities, while the equivalent value for concentrations was 14.50%.

The Predicted Percentage Dissatisfied (PPD) index produced by Fanger and given in the American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) guide (ASHRAE, 1997a) is widely used in assessing thermal comfort (Memarzadeh et al., 2000). This index can be estimated by equations that are based on an empirical investigation of how people react to differing environments. In CFD simulation, PPD can be calculated for each cell in turn and a volume weighted average can be produced for a specific zone. It is well-known that each individual has a different perception of the climate in a building and that any given climate is unlikely to be considered satisfactory by all. In fact, 80% occupant satisfaction is considered good, or a PPD of less than 20%. The PPD is directly related to the Predicted Mean Vote (PMV). While PPD provides the information as to whether or not the environment is likely to be acceptable, PMV tells us what the problem is—whether it is too hot or too cold—when the number dissatisfied is too large. The equations implemented in the analysis shown here are taken from Fanger’s equations for PMV and PPD as given in BS EN ISO 7730: 1995.

Definitions

$$PMV = (0.303e^{0.036M} + 0.028)((M - W) - 3.05x10^{-4}[5733 - 6.99(M - W) - p] - 0.42[(M - W) - 58.15]1.7x10^{-5}(5867 - p) - 0.0014M(34 - t) - 3.96x10^{8}f_{cl}(tcl - t) + 273)^{3} - (t + 273)^{3})$$

where

$$tcl = 35.7 - 0.028(M - W) - I_{d}(3.96x10^{8}f_{cl}(tcl + 273)^{3} - (t + 273))^{3} + f_{cl}(tcl - t)$$

$$h_{c} = 2.38(tcl - t)^{0.25}$$

$h_{c} = 12.1v^{0.5}$

Figure 2

Super-imposed grid of cells for calculation.
whichever is greater
\[ f_i = 1.00 + 1.29I_i \text{ for } I_i \leq 0.078 \text{ m}^2\text{KW}^{-1} \] or
\[ f_i = 1.05 + 0.645I_i \text{ for } I_i > 0.078 \text{ m}^2\text{KW}^{-1} \]
PPD = 100 − 95e\(^{-n}\)
\[ \text{where } n = 0.03353\text{PMV}^4 + 0.2179\text{PMV}^2 \] (3)

List of Symbols
PMV = Predicted Mean Vote
PPD = Predicted Percentage Dissatisfied
M = Metabolic rate (W/m\(^2\) of the body area)
W = External work (W/m\(^2\) of the body area [ = 0 in most cases])
I\(_{cl}\) = thermal resistance of clothing (m\(^2\)KW-1)
f\(_{cl}\) = Ratio of clothed surface area to nude surface area
t\(_a\) = Air temperature (°C)
t\(_r\) = Mean radiant temperature (°C)
v = Air velocity relative to the body (m/s-1)
p\(_a\) = Partial water vapor pressure in Pa
hc = Convective heat transfer coefficient (Wm\(^2\)K)
t\(_{cl}\) = Clothing surface Temperature (°C)

Model Setup

A generic laboratory that had one island bench, two wall benches, one two-way throw, and two one-way throw chilled beams was developed as the laboratory model for this study as shown in Figure 3. Using the same chilled beams, six cases were studied at different primary supply flow rates and with and without a fume hood fitted, as listed in Table 1. The supply angle of the beams was 45° from the ceiling for all cases. In Cases 4 through 6, a fume hood was located against the wall opposite the windows. These cases were designed to investigate the effects of the chilled beams on the fume hood containment, as well as the effectiveness of the beams in removing the contaminant from the room if there was a contaminant spill on the bench top.

The induced flow rate of the chilled beams is dependent upon the primary flow rate and the dimension and type of the nozzle through which primary air is supplied to the mixing zone (Figure 1). This study does not take into account geometric details to accurately calculate the pressure in the mixing zone and, therefore, to determine the exact induced airflow rate for each case. In this study, typical ratios of the induced flow rate to the primary flow rate were employed. The temperature drop of the induced flow through a cooling coil was treated in the same way as this parameter could be regulated to the required value by adjusting the cooling water flow rate. The same beam geometry was used for different airflow rates, which makes sense within a narrow range of values. In reality; however, the geometry of the beam and some of the system operating parameters such as air temperature, water temperature, nozzle quantity and type need to be changed to achieve the mix airflow for total load capacity that the room requires.

The following assumptions were made in the model laboratory for this study.
- **Room dimensions**: 6.35m (20’ 10”) wide, 11m (36’)
long and 3.2m (12’ 6”) high.

- **Ventilation system:** Two one-throw chilled beams and one two-throw beam on the ceiling with ceiling exhausts (one or two, depending on the total exhaust flow rate) as shown in Figure 2.

- **Door Gaps:** There was a 200 CFM inflow through the door gaps due to infiltration.

- **Supply temperature of primary air:** Primary air temperature remained at 13.3°C (56°F). After mixing with the induced air from the room, the supply air temperature was in the range of 59.4-62.6°F.

- **Heat sources:** The total heat generation from the bench devices was 5808W. The total lighting heat sources from the ceiling and the workbench was 2083W.

- **Occupants:** Seven occupants each generating 80W sensible heat.

- **Environment:** The external ambient was assumed to be 31.5°C (88.7°F) with an external convective heat transfer coefficient of 6W/m-K. Solar loading from the south-facing windows on the external wall was divided as 1160W transmitted into the room and 1243W absorbed by the glass. Another 30W was conducted through the external wall section. The ceiling, floor and walls were assumed to be adiabatic. Surface-to-surface radiation was not modeled in this study.

For the sake of comparison, this same laboratory with a ceiling diffuser system and ceiling mounted radiant cooling panels was also numerically investigated using 16 different layouts of cooling panels and supply flow rates (see the details of the 16 cases in Table 3 in the results section). The cooling panels were above the bench top and aisle shown in Figure 4. The set mounted above the bench top includes three panels. The central panel is 0.6m (23.5”) wide, and the two against the side walls are 0.3m (12”) wide. The other set was mounted above the two aisles. These cooling panels were maintained at 13.9°C (57°F) temperature. There were also bench exhausts installed in these 16 cases. The bench exhausts were configured with continuous slots mounted beneath the shelves of the bench and along the length of the benches. The supply temperature was 11.1°C (52°F), 2.2°C lower than that of the chilled beams cases.

Great care was taken with regard to correctly model the chilled beams, fume hood and the numerical grid for CFD. The number of grid cells used in these cases was in the order of 800,000 cells. Grid dependency tests were performed to ensure that the results were appropriate and would not vary upon increasing the grid density. In particular, attention in the tests was directed at areas containing the main flow, or heat sources in the room, for example, the chilled beams and the area close to the glazing, as well as areas of largest flow, or temperature gradients and the flow through the door cracks. Grid was added appropriately in these regions and their surroundings.

### Results

In this section, the air temperature and PPD are discussed in detail since they include the effects of all important parameters on thermal comfort such as metabolic rate, external work, clothing, local air velocity and mean radiant temperature as shown in Equations (2) and (3). Two sets of occupied zone, the walking zone and the bench zone, are defined for evaluating and comparing the performance of different ventilation schemes. The walking zone covers the areas of aisles and the doorways from the floor to 1.8m (71”) above floor level and the bench zone includes all benches from the top of the benches to 1.8m (71”) above floor level, as highlighted in Figures 5 and 6, respectively. The simulation results are discussed with respect to thermal comfort and air quality.

### Thermal Comfort

The simulation results, mainly the average PPD and temperature in the two occupied zones, are summarized in Tables 2 and 3 for the chilled beam cases and for the ceiling diffuser, with and without cooling panels respectively. The average PPD for the chilled beam cases together with three ceiling diffuser cases without cooling panels is also plotted in Figure 7 to show the trend. The average air temperature in the occupied zones in the chilled beam cases is 16°C lower than that of the cases.
at the same supply flow rate using ceiling diffusers plus cooling panels, although the primary supply air temperature is 2.2°C higher. The average PPD in occupied zones falls below 15% for all cases with chilled beams even at 4 ACH. The chilled beams appear to work well with variable primary flow rate as the variation of the primary flow rate from 10 ACH to 4 ACH does not have a substantial impact on thermal comfort in the occupied zone. At the lowest flow rate considered, 4 ACH (Case 3), the average PPD with chilled beams is noticeably lower than that of the ceiling diffuser cases of the same flow rate (C-Cases 13 through 16), especially in the bench zone where the average PPD is greatly improved by chilled beams. Bench exhausts were used in the ceiling diffuser cases. The results indicate that with chilled beams, the cooling capacity can be well provided using a water-cooled coil system, and the primary airflow of the system only needs to satisfy the indoor air quality requirements.

**Figure 4**
Two sets of ceiling mounted cooling panels.

Two Aisle Panels, 0.6m (23.5”) x 7.3m (24’)

Three Aisle Panels
6.5m (21’ 4”) long

**Figures 5 and 6**
**Figure 5:** Walking Zone—Defined as the volume from the floor to 1.8m (71”) above the floor in the five highlighted areas. **Figure 6:** Bench Zone—Defined as the volume above the bench top to 1.8m (71”) above the floor in the four highlighted areas.
Radiant cooling panels rely mainly on the direct cooling of occupants by radiative heat transfer. When cooling panels are used, sensible heat is removed from the room by both ventilation and radiation. Through radiative heat transfer, people in the room emit heat that is absorbed by the radiant cooling panel surface. Therefore, a similar level of thermal comfort can be achieved with higher average air temperature in the occupied zone than with a chilled beams case, (see Case 3 and C-Case 8). It is noticed that the average PPD in the two occupied zones at 6 ACH drops below 20%, the designed thermal comfort condition, with any one of the three cooling panel arrangements. The results also indicate that the two sets of cooling panels cannot bring the PPD below 20% when the ventilation flow rate is reduced to 4 ACH, the minimum ventilation requirement for laboratories, unless more cooling panels are installed. With chilled beams, very satisfactory PPD (averaging around 10%) in the occupied zones can be achieved at as low as 4 ACH. To obtain a similar level of thermal comfort, 6 ACH is required with two sets of cooling panels and bench exhausts (see C-Case 8 in Table 3).

The temperature and velocity distribution in a vertical plane half way through the length of the room are presented in Figures 8 and 9, respectively, for chilled beams at 8 ACH. The temperature in the room is quite uniform except in the region around the heat sources in the bench top. The temperature stratification from the floor to the ceiling is less than 2°C, which is regarded as one of the benefits of using the chilled beams. While occupants can be thermally comfortable overall, they may still experience discomfort from drafts on a specific part of their body. Occupants’ experience of draft depends on air temperature, air velocity, and turbulence intensity. In general, air temperatures within the comfort zone and air velocities below 0.25 m/s (for summer) are considered to meet the thermal comfort requirement (ASHRAE, 1997b). ASHRAE allows for higher air veloci-

### Table 2

*Chilled Beams—Air temperature and PPD in the occupied zones.*

<table>
<thead>
<tr>
<th>Without fume hood</th>
<th>Primary flow rate CFM</th>
<th>Induced Air flow rate CFM</th>
<th>Ceiling exh. CFM</th>
<th>Hood exh. CFM</th>
<th>Average</th>
<th>Average PPD (%)</th>
<th>Return</th>
<th>Exh Air T (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1, 8 ACH</td>
<td>970</td>
<td>1746</td>
<td>15.3</td>
<td>-885</td>
<td>0</td>
<td>21.9</td>
<td>11.0</td>
<td>13.2</td>
</tr>
<tr>
<td>Case 2, 8 ACH</td>
<td>730</td>
<td>1971</td>
<td>15.2</td>
<td>-630</td>
<td>0</td>
<td>22.0</td>
<td>11.3</td>
<td>11.9</td>
</tr>
<tr>
<td>Case 3, 4 ACH</td>
<td>485</td>
<td>2280</td>
<td>15.4</td>
<td>-885</td>
<td>0</td>
<td>22.6</td>
<td>9.3</td>
<td>10.2</td>
</tr>
<tr>
<td>With fume hood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 4, 10 ACH</td>
<td>1210</td>
<td>2299</td>
<td>17.0</td>
<td>-310</td>
<td>1100</td>
<td>22.2</td>
<td>10.1</td>
<td>11.4</td>
</tr>
<tr>
<td>Case 5, 8 ACH</td>
<td>970</td>
<td>1746</td>
<td>15.3</td>
<td>-320</td>
<td>850</td>
<td>22.2</td>
<td>10.7</td>
<td>9.5</td>
</tr>
<tr>
<td>Case 6, 8 ACH</td>
<td>730</td>
<td>1971</td>
<td>15.2</td>
<td>-800</td>
<td>-330</td>
<td>22.3</td>
<td>10.0</td>
<td>9.2</td>
</tr>
</tbody>
</table>

### Table 3

Sixteen ceiling diffuser cases using different layouts of radiant cooling panels.

<table>
<thead>
<tr>
<th>Cooling panels</th>
<th>ACH</th>
<th>Bench exh. CFM</th>
<th>Ceiling exh. CFM</th>
<th>Average</th>
<th>Average PPD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Case1 No panel</td>
<td>8</td>
<td>-800</td>
<td>-370</td>
<td>24.0</td>
<td>7.6</td>
</tr>
<tr>
<td>C-Case2 Bench panels</td>
<td>8</td>
<td>-800</td>
<td>-370</td>
<td>23.5</td>
<td>7.3</td>
</tr>
<tr>
<td>C-Case3 Aisle panels</td>
<td>8</td>
<td>-800</td>
<td>-370</td>
<td>23.5</td>
<td>7.3</td>
</tr>
<tr>
<td>C-Case4 Bench &amp; Aisle</td>
<td>8</td>
<td>-800</td>
<td>-370</td>
<td>23.1</td>
<td>7.3</td>
</tr>
<tr>
<td>C-Case5 No panel</td>
<td>6</td>
<td>-800</td>
<td>-130</td>
<td>26.4</td>
<td>25.1</td>
</tr>
<tr>
<td>C-Case6 Bench panels</td>
<td>6</td>
<td>-800</td>
<td>-130</td>
<td>25.5</td>
<td>16.0</td>
</tr>
<tr>
<td>C-Case7 Aisle panels</td>
<td>6</td>
<td>-800</td>
<td>-130</td>
<td>25.4</td>
<td>14.9</td>
</tr>
<tr>
<td>C-Case8 Bench &amp; Aisle</td>
<td>6</td>
<td>-800</td>
<td>-130</td>
<td>24.9</td>
<td>12.3</td>
</tr>
<tr>
<td>C-Case9 No panel</td>
<td>5</td>
<td>-600</td>
<td>-208</td>
<td>27.4</td>
<td>18.7</td>
</tr>
<tr>
<td>C-Case10 Bench panels</td>
<td>5</td>
<td>-600</td>
<td>-208</td>
<td>26.7</td>
<td>13.4</td>
</tr>
<tr>
<td>C-Case11 Aisle panels</td>
<td>5</td>
<td>-600</td>
<td>-208</td>
<td>26.5</td>
<td>12.3</td>
</tr>
<tr>
<td>C-Case12 Bench &amp; Aisle</td>
<td>5</td>
<td>-600</td>
<td>-208</td>
<td>26.1</td>
<td>10.0</td>
</tr>
<tr>
<td>C-Case13 No panel</td>
<td>4</td>
<td>-600</td>
<td>-86</td>
<td>28.8</td>
<td>28.1</td>
</tr>
<tr>
<td>C-Case14 Bench panels</td>
<td>4</td>
<td>-600</td>
<td>-86</td>
<td>28.0</td>
<td>19.5</td>
</tr>
<tr>
<td>C-Case15 Aisle panels</td>
<td>4</td>
<td>-600</td>
<td>-86</td>
<td>27.9</td>
<td>18.5</td>
</tr>
<tr>
<td>C-Case16 Bench &amp; Aisle</td>
<td>4</td>
<td>-600</td>
<td>-86</td>
<td>27.5</td>
<td>15.0</td>
</tr>
</tbody>
</table>
ties in warm, humid conditions as some research suggests that occupants welcome the cooling effect the higher velocities provide. As chilled beams operate at a high supply flow rate due to the considerably high flow rate of induced air, drafts can become a factor in causing thermal discomfort. At 8 ACH, the average velocity in the occupied zones with chilled beams is 0.24m/s. This is considered to be comfortable for an air temperature between 23-24°C. When the air temperature is lower, this air velocity could be high, particularly at some spots where the local velocity is around 0.34m/s, as shown in Figure 8. The air velocity and local temperature variations are responsible for causing 11% PPD in the walking zone for the case of 8 ACH. The results also indicate that the air temperature at ceiling exhausts is about 1-2°C higher than the recirculation air temperature leaving the room. This is due to the short-circuiting of the induced air, which can be improved by adjusting the supply angle of the diffusers.

Air Quality and Hood Containment

The discussion in this section focuses on the three chilled beam cases in the presence of a fume, Cases 4 through 6.

Fume Hood Containment

The fume hood located in the corner opposite to the windows (Figure 3) is a three-sided enclosure with an adjustable front sash opening. The fume hood is designed to capture and exhaust hazardous fumes generated inside its enclosure by extracting air from the back of the hood to the outside of the building. Since exposure to volatile chemicals constitutes one of the top health and safety hazards to laboratory workers, a fume hood operates as a principle safety device in a laboratory setting. According to the Federal Occupational Safety and Health Administration (OSHA) the face velocity of the hood should be in the range of 0.3m-0.5m/s (60-100 fpm). The sash opening in this study was adjusted to obtain a face velocity of 0.5m/s for all three cases. As the room geometry, ventilation system, diffuser/exhaust locations and operational procedures within a laboratory all affect airflow, it is necessary to assess how chilled beams in the laboratory influence the containment of the hood. In an ideal case, the contaminants generated from a source at the sash opening would be nearly 100% removed by the hood. In reality, however, the contaminants leak backwards into the room due to turbulent diffusion, even if there is no recirculation at the sash opening. The body movements in front of the hood can also increase turbulence and reduce effectiveness of hood containment. The lower the contaminant leakage, the better is the hood containment. Quantitative fume hood containment tests reveal that the concentration of contaminants in the breathing zone can be 300 times higher from a source located at the front of the hood face than from a source placed at least six inches back (National Research Council, 1995). This concentration declines more as the source is moved farther towards the back of the hood.

In this study, the sash opening was assumed to be filled with contaminants released towards the inside of the hood to represent a worst-case scenario. The contaminants mass leaking back into the room were represented through an imaginary box that was placed in front of the hood extending 12” outside the sash opening as...
shown in Figure 10. The total contaminants leaking into the room was the summation of the net leakage at the five faces of the imaginary box. The leakage factor, defined as the fraction of contaminant mass flow rate leaking from the hood to the room against the contaminant mass removed by the hood exhausts, can be used to evaluate the hood containment. This definition has the same meaning as the Box leakage factor outlined by Memarzadeh (Memarzadeh, 1996).

The leakage factor of Cases 4 to 6, shown in Figure 11, varies from 0.00139 to 0.00277. In a concurrent study on hood containment, the leaking factor for a case at 13 ACH with ceiling diffuser was in the range of 0.00183 to 0.00212. The slightly higher leaking factor when chilled beams are operating can be due to the higher turbulence level in the room caused by quite high induction flow rates in addition to the primary flow rates.

**Gas and Airborne Particle Removal Effectiveness of a Chilled Beam System with Fume Hood**

In order to examine how the chilled beam system functions in removing contaminants from the room, a chemical spill on the bench top at two locations was considered. The chemical spill was modeled as a source located at the center of the affected bench, either at Location 1 or at Location 2, as highlighted in Figure 12. The concentration was assumed to be 1x10^6 ppm at the top of the contaminants’ source. With the existence of the source, the contaminants were dispersed in the room by convection and diffusion and the distribution of the contaminants is shown in Figure 13.
contaminant concentration was computed in the CFD simulations. The removal effectiveness of the chilled beam system was evaluated by the average concentration in the occupied zone as presented in Figure 13. The concentration at the breathing level in front of the four occupants positioned closer to the source, as marked in Figure 12, were also monitored and plotted in Figures 14 and 15 for the two assumed source locations.

Figure 13 shows that the concentration level is lower in the walking zone than in the bench zone for all cases and the average concentration increases when the primary flow rate decreases. Unlike the average concentration, the local concentrations at the breathing level of the four occupants being monitored are not necessarily increased when primary flow rate decreases. For example, Figure 15 shows that for source Location 2, the case with 6 ACH has the lowest local concentration in front of occupant 4. As the induced flow is relatively high in the chilled beam system, the flow pattern and the resultant concentration distribution can be affected more by induced flow rate change than by the primary flow rate change. Table 4 presents the range of average concentration in the occupied zone for the two source locations when using chilled beams, or a ceiling diffuser system. For both systems, the fume hood is operating. The data indicate that the removal effectiveness of the chilled beams is in the same level of the ceiling diffusers even though the primary flow rate of the chilled beams is lower. The chilled beam system in the cases studied seems to generate a better mix condition in the room than ceiling diffusers do, which improves the removal effectiveness as a result.

Figure 10
Sash opening and the imaginary box in front of the sash opening.

Figure 11
Hood leaking factors for Cases 4 through 6.
Operating Cost Reduction

Table 5 presents the annual cooling costs for a typical 70m² lab for the chilled beam cases. The following conditions/assumptions are used in this calculation.
- The outdoor temperatures and ambient condition are taken from weather data in Washington, DC.
- The cooling season is considered to be 4,489 hours annually.
- The percentage of outdoor air is 100% for all cases.
- Supply air temperature is 13.3°C (56°F).
- Cooling load per CFM is considered to be the difference in air enthalpy when entering and leaving the HVAC system. Perfect duct insulation is assumed.
- The ventilation flow rate (CFM) shown in Table 4 is the flow rate required during the peak load of the day. The average cooling load of a day is assumed to be 64.3% of the day’s peak load, as is the ventilation flow rate used in the cost calculation.
- The cost of electricity is 0.1$/KWH, fuel is 8.0$/MMBtu; chilled water generation efficiency is 1.0KW/TON; fan efficiency is 68%.

Figure 12
Locations of contaminant sources and the four positions being monitored.

Figure 13
Average contaminant concentration in occupied zones with two source locations for cases with fume hood.
The simulation results demonstrate that with a fume hood, the ventilation flow rate required in chilled beams can be as low as 6 ACH for equipment-intensive laboratories to be thermally comfortable while still meeting the air quality requirement. A concurrent study reveals that when using ceiling diffusers without bench exhausts and cooling panels, the required flow rate to achieve a similar level of thermal comfort and air quality can be as high as 13 ACH. With the reduced ventilation flow rate, a 22.5% saving in annual energy cost for cooling and ventilating a typical laboratory in the Washington, DC area can be achieved as shown in Figure 16. In this calculation, 70% and 100% of outdoor air are assumed for ceiling diffusers at 13 ACH and chilled beams at 6 ACH. A fume hood is present in both cases.

Conclusions

The following conclusions can be drawn from this study:
1. Chilled beams improve thermal comfort, and can be operated at as low as 4 ACH (without a fume hood in the laboratory) while maintaining very satisfactory average PPD (around 10%) in the occupied zones. To obtain a similar level of thermal comfort, 6 ACH is required for ceiling diffuser system with two sets of cooling panels and bench exhausts.
2. The presence of an operational fume hood slightly improves the thermal comfort in the room.
3. The average concentration in the occupied zone caused by the bench top spills increases when the primary
flow rate decreases, but is not very sensitive to the change of primary air flow rate. The chilled beams improve the removal effectiveness of gases and airborne particles by generating a better mixed condition in the room than ceiling diffusers.

4. The chilled beams in the cases studied are seen to have an insignificant effect on the hood containment.

5. Using chilled beams with a fume hood, satisfactory thermal comfort and air quality can be achieved at 6 ACH (100% Outside Air) in comparison with an all-air ceiling diffuser ventilation system at 13 ACH (70% Outside Air), which indicates a 22.5% saving in annual energy costs for cooling and ventilating a typical lab in the Washington, DC area.

It should be noted that the use of chilled beams is not intended to be applicable to all types of laboratories and should not override the contaminant controls that are appropriate for this type of laboratory, particularly with respect to the use of appropriate biosafety cabinets (BSCs) and/or fume hoods, and the handling of hazardous materials on the workbenches. Finally, the usefulness of the chilled beam system may not be beneficial from a cost standpoint in scenarios where the room flow rate is already low, and energy costs are relative to other occupied spaces.

### Table 4
Comparison of Chilled beam system and ceiling diffuser system on average contaminant concentration in occupied zones for cases with fume hood.

<table>
<thead>
<tr>
<th></th>
<th>Walking Zone</th>
<th>Bench Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceiling diffuser at 13 ACH</td>
<td>940-1500</td>
<td>1470-2240</td>
</tr>
<tr>
<td>Chilled beams at 10-5 ACH</td>
<td>880-1820</td>
<td>1440-2430</td>
</tr>
</tbody>
</table>

### Table 5
Annual energy cost for cooling a typical lab located in Washington, DC.

<table>
<thead>
<tr>
<th>Without fume hood</th>
<th>Primary flow rate CFM</th>
<th>Induced Air flow rate CFM</th>
<th>Total Air flow rate CFM</th>
<th>Supply T °F</th>
<th>Air Delta-T through Coil d°F</th>
<th>OA %</th>
<th>Energy Cost For Cooling</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Air</td>
<td>Induced Air</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1, 6 ACH</td>
<td>970</td>
<td>1746</td>
<td>2716</td>
<td>59.5</td>
<td>9.9</td>
<td>100</td>
<td>$2,040</td>
<td>$483</td>
</tr>
<tr>
<td>Case 2, 6 ACH</td>
<td>730</td>
<td>1971</td>
<td>2701</td>
<td>59.4</td>
<td>10.7</td>
<td>100</td>
<td>$1,936</td>
<td>$500</td>
</tr>
<tr>
<td>Case 3, 4 ACH</td>
<td>495</td>
<td>2280</td>
<td>2765</td>
<td>59.7</td>
<td>10.5</td>
<td>100</td>
<td>$1,020</td>
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<th>With fume hood</th>
<th>Primary flow rate CFM</th>
<th>Induced Air flow rate CFM</th>
<th>Total Air flow rate CFM</th>
<th>Supply T °F</th>
<th>Air Delta-T through Coil d°F</th>
<th>OA %</th>
<th>Energy Cost For Cooling</th>
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### Figure 16
Saving in annual cooling cost for a typical laboratory in the Washington, DC area.
References


Biosafety, Occupational Health and Nanotechnology

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Abstract

Nanotechnology promises to improve the quality of human life, but it has also provoked concerns about potential adverse health effects on workers, the environment and consumers. Effective risk assessment and risk management of nanotechnology requires: 1) knowing how engineered nanoscale particles (NPs) can gain entry into the human body (routes of exposure); 2) knowing whether engineered NPs can migrate from their point of entry to other locations in the body (translocation); 3) determining what adverse biological effects may occur in response to engineered NP exposure (toxicity); 4) knowing which measurement of exposure and dose correlates best to toxicity (exposure and dose metrics); and 5) knowing how best to monitor exposed populations to detect the occurrence of any adverse health effects (health surveillance). This article reviews what is currently known about potential health risks to workers from exposure to engineered NPs, as well as the best methods to control those risks, in order to ensure that their use in the laboratory and industry conforms to the best principles of occupational health and biosafety.

Introduction

Nanotechnology refers to a new set of technologies that are used to develop nanometer-sized structures and devices (<100 nanometers in at least one dimension) with unique, or enhanced properties for commercial application (NSTC, 2004). At the nanometer scale, certain materials exhibit new properties not exhibited at the macro scale. For instance, materials that were not reactive at the macro scale become highly reactive at the nanoscale
lacks, both actual and perceived, be identified swiftly and managed responsibly if the promise of nanotechnology is to be realized.

Effective risk assessment, risk characterization and risk management of nanotechnology requires: 1) knowing how engineered nanoscale particles (NPs) gain entry into the human body (routes of exposure); 2) knowing whether engineered NPs can migrate from their point of entry to other locations in the body (translocation); 3) determining what adverse biologic effects may occur in response to engineered NP exposure (toxicity); 4) knowing which measurement of exposure and dose correlates best to toxicity (exposure and dose metrics); and 5) knowing how to best monitor exposed populations to detect the occurrence of any adverse health effects (health surveillance).

At the present time, we are just beginning to develop answers to these important questions that will help us develop effective risk management for engineered NPs. We do have substantial information about other NPs, which have been incidentally generated by anthropogenic processes involving industrial processes, combustion, welding, automobile and diesel engines operation (incidental NPs); created by natural processes such as volcanic activity, or synthesized by living systems, such as proteins and viruses (natural NPs).

Drawing upon our knowledge of routes of exposure, toxicity and health effects seen from human exposure to incidental NPs, we review in this article what is currently known about the potential health risks to workers from exposure to engineered NPs and the best available methods to control those risks in order to ensure their use in the laboratory and in industry conforms to the best principles of occupational health and biosafety.

Routes of Exposure

Inhalation

The most common route of exposure to any aerosol particle in the workplace, including a NP, is through inhalation. In this route, the deposition of NPs in the respiratory tract is determined by the aerodynamic diameter of a stand-alone particle, or of a NP agglomerate, in which many weakly attached discrete NPs form a particle larger than 100 nm. However, agglomerates have the potential to deagglomerate during, or after deposition in the respiratory tract. Discrete NPs are deposited in all regions of the lung, including the deep alveolar region, to a greater extent than larger respirable particles (ICRP, 1994). Deposition increases with exercise due to an increase in breathing rate and a change from nasal-to-mouth breathing (Jaques & Kim, 2000; Daigle et al., 2003). Deposition also increases among persons with existing lung diseases, or conditions (Brown et al., 2002). Based on animal studies, discrete NPs may enter the bloodstream from the lungs and translocate to other organs (Takenaka et al., 2001; Nemmar et al., 2002; Oberdörster et al., 2002).
Inhalation exposure is also an important route for contracting viral diseases such as influenza. It is believed that in this route of exposure, viruses are carried in a liquid-matrix of sub-micron particles called droplet nuclei, which are generated by expiration, coughing, and sneezing. This route is also employed for intentional exposure to attenuated viruses mimicking the natural route of influenza infection in some nasal-spray vaccines against influenza (Maassab et al., 1990). The respiratory route is also under active investigation as a potential route of drug delivery using engineered NPs. Coupling of drug molecules with carrier-NPs may allow controlled deposition rates via inhalation route and facilitate translocation to the blood stream (Vogel & Baird, 2005).

**Ingestion**

Ingestion may also accompany inhalation exposure, because particles that are cleared from the respiratory tract via the mucociliary escalator may be swallowed (ICRP, 1994). In addition, engineered NPs can enter the digestive tract by ingestion of contaminated food or water and by hand-to-mouth transfer from contaminated surfaces. The ability of mucosal membranes and the gastrointestinal tract to absorb and, in some cases, facilitate systemic distribution of NPs, such as liposomes, proteins and viruses (e.g., rotavirus, hepatitis E) is well-known. In addition, it has been shown that inorganic particles, such as 500 nanometer (nm) titanium dioxide (Jani et al., 1994) and nanoscale gold (Hillery, 2001), have the potential to cross the digestive tract lining and translocate to systemic organs such as the liver, spleen, lung and peritoneal tissues. There is also evidence that smaller particles can be transferred more readily than their larger counterparts across the intestinal wall (Behrens et al., 2002). These natural processes are presently under investigation for potential applications in developing nanoscale vehicles for oral drug and nutrients delivery: poly(DL-lactide-co-glycolide)-coated particles (Brayden & Baird, 2001), liposomes (Hussain et al., 2001), fatty acid polymer particles (Mathiowitz et al., 1997), and virosomes (Rae et al., 2005). Such nanoscale formulations have the potential to improve the solubility of poorly soluble drugs by enveloping them in an amphiphilic coating; the permeability through bioconjugation with polymers facilitating trans- and para-cellular transfer and through nanoscale size and morphology, which could be recognized and absorbed by intestinal cells; and the stability through controlled degradation, adhesion to intestinal mucosa and availability of intestinal enzymatic inhibitors. For example, intact, biologically active insulin and pancreatic ribonuclease can be delivered into the blood circulation through oral administration in the presence of bile acid and protease inhibitor (Ziv et al., 1987).

**Dermal**

Dermal exposure can be another route for NPs to gain entry into the human body. Penetration of intact skin can occur through a number of pathways, including sweat ducts, stratum corneum via inter- or intracellular modes and hair follicles. The ability of nanoscale particles to cross the skin’s outer layer of stratum corneum remains a subject of intense study and debate. Some studies indicate that particles as large as 1000 nm can penetrate human skin upon flexing in vitro (Tinkle, 2003), while other studies show that nanoscale titanium dioxide remained on the outermost layer of unperturbed human skin in vivo after six hours with none detected in the deeper stratum corneum, epidermis or dermis (Schulz et al., 2002). A recent study showed that mechanical flexing of skin can increase the rate and the amount at which fullerene-based amino acid engineered NPs can penetrate through the skin (Rouse et al., 2007).

From biological examples, it is well known that only small lipophilic molecules can penetrate skin, while proteins are believed to be unable to pass through this tough barrier. Physical approaches, including electric fields, ultrasound, jet injectors, micro-needles and thermal ablation have been shown to aid in breaching the skin barrier (Prausnitz, 2006). Recently, transdermal delivery of intact, biologically active protein medications such as insulin has been shown possible in the presence of phage peptide chaperones (Chen et al., 2006). It appears that the mechanism of penetration is not specific to insulin and involves interactions between phage peptide and the skin facilitating transfollicular route of insulin transport across the skin.

A number of viruses, such as the herpes virus, are known to cross the skin and mucosal barrier by entering nerve endings and translocating via an axoplasmic route to the neuronal soma ending in the brain. Similarly, animal studies have shown that discrete insoluble NPs, from 20 to 500 nm diameter, deposited in the nasal region may be able to enter the brain by translocation along the sensory nerves, including olfactory and trigeminal nerves (Oberdörster et al., 2004; Oberdörster et al., 2005; De Lorenzo, 1970; Adams & Bray, 1983; Hunter & Dey, 1998).

**Parenteral**

NPs can be also introduced into human bodies via the parenteral route either incidentally through cuts and other damage to intact skin, or intentionally for drug delivery, medical imaging, or other applications. Engineered NPs for drug applications can deliver markedly improved characteristics: 1) enhanced solubility especially for hydrophobic entities; 2) increased stability through coatings capable of avoiding the immune system; 3) improved specificity through multifunctional capabilities and active and passive targeting; and 4) the enhanced ability to penetrate specific barriers like the blood-brain barrier. Engineered NPs that enter the body parenterally can interact with plasma proteins in trivial ways, such as covalently bonding to proteins without changing the function of the protein, and non-trivially, by interacting
with the body’s systems similar to interactions characteristic of certain natural nanoscale particles, such as proteins and viruses.

Translocation of Nanoparticles

Deagglomeration, translocation, and distribution play key roles in the fate of NPs once they gain entrance into the human body. NPs, which are smaller than 20 nm, can transit through blood vessels. Magnetic nanoparticles, for instance, can image metastatic lesions in lymph nodes, because of their ability to exit the systemic circulation through the permeable vascular epithelium (Bogdanov et al., 2005). Some NPs can also penetrate the blood-brain barrier through paracellular movement, passive diffusion, transport and endocytosis (Lockman et al., 2003; Kreuter, 2004). Translocated NPs can become biopersistent in the body if the immune system fails to recognize them as foreign bodies, or they can potentially be cleared from the body because of biodegradation, or their higher solubility compared to larger sized particles of the same chemistry (Borm et al., 2006).

Toxicity of Nanoparticles

Incidental NPs

The results of animal and human studies on exposure and response to incidental NPs, or other respirable particles, provide a basis for preliminary estimates of the possible adverse health effects from exposures to engineered NPs (Gwinn & Valliyathan, 2006). Perhaps the most important study to be conducted in the last 10 years has shown a link between exposure to a high level of urban air pollution, including incidental NPs, and increased morbidity and mortality due to cardiovascular disease (Pope et al., 2004). More specifically, a correlation was found between number concentration of incidental NPs in the ambient air and blood biomarkers of inflammation and endothelial dysfunction and coagulation among patients with coronary heart disease (Rückerl et al., 2006). Other examples of observed correlations between exposures to incidental NPs and adverse health effects include: exposures to diesel exhaust particulate have been correlated with an elevated risk of lung cancer (Steenland et al., 1998; Garshick et al., 2004), while exposures to welding fumes have been found to cause respiratory effects, such as bronchitis, airway irritation, lung function changes, and a possible increase in the incidence of lung cancer (Antonini, 2003). Occupational exposure to nanometer-sized polytetrafluoroethylene (PTFE) fume (generated at temperatures more than 425 degrees centigrade) is known to be highly toxic to the lungs. Freshly-generated PTFE fume caused hemorrhagic pulmonary edema and death in rats exposed to less than 60 \( \mu \text{g/m}^3 \) (Oberdörster et al., 1995). In contrast, aged PTFE fume was much less toxic and did not result in mortality, which was attributed to the increase in particle size due to agglomeration and to changes in surface chemistry (Johnston et al., 2000; Oberdörster et al., 2005). Human case studies have reported pulmonary edema in workers exposed to PTFE fume, and an accidental death in a worker when equipment malfunctioned, caused overheating of the PTFE resin and release of the PTFE pyrolysis products in the workplace (Lee et al., 1997). While incidentally-generated PTFE fume differs from engineered NPs, these studies illustrate the size-dependent properties and surface activity of NPs that may be associated with an acute toxic hazard.

Engineered NPs

When it comes to evaluating the health effects of natural nanoscale materials synthesized by living organisms, a wide range of responses exist from the benign and beneficial, such as those to insulin and growth hormone, to the adverse and even lethal effects from protein biotoxins. Similarly, engineered nanoscale materials can potentially elicit the full range of health responses observed for natural and incidental nanoscale materials. Some of these responses could be also used for beneficial medical applications. For example, a recent report describes a nontoxic and non-immunogenic liquid containing self-assembling peptides, which form a nanofiber barrier stopping bleeding within 15 seconds of application to a wound (Ellis-Behnke et al., 2006).

A single-walled carbon nanotube (SWCNT) is an example of engineered nanoscale material whose toxicological properties have been studied extensively. For example, the National Institute for Occupational Safety and Health (NIOSH) researchers recently reported adverse lung effects following pharyngeal aspiration of SWCNTs in mice using doses between 10-40 \( \mu \text{g/mouse} \) (approximately 0.5-2 mg/kg body weight) (Shvedova et al., 2005). The findings showed that exposure to SWCNTs in mice lead to transient pulmonary inflammation and oxidative stress, decreased pulmonary function, decreased bacterial clearance and the early onset of progressive, interstitial fibrosis. Deposition of agglomerates resulted in the development of granulomas, while deposition of more dispersed nanotube structures resulted in the rapid development of interstitial fibrosis within seven days, which progressed over a 60-day post-exposure period. SWCNT was found to be more fibrogenic than an equal mass of either ultrafine carbon black or fine quartz.

Descriptors of Nanoparticle Toxicity

A number of reviews on the health effects of NPs have highlighted the unique features of NPs, which distinguish them from either conventional molecular species, or larger particles of bulk materials (Ostiguy et al., 2006; Nel et al., 2006; NSTC, 2006). The three features—size, surface, and shape—discussed below, either separately, or in combination, may ultimately be shown in
the inflammatory response to inhaled TiO₂ of particles. Indeed, it was observed in animal studies that toxic response should correlate with the total surface area particles are determined by interactions occurring at the interface between particles and biological systems, then toxic response should increase as particle size decreases for the same mass dose. Such a dependence was observed for a number of poorly soluble low toxicity materials (Oberdörster, 2000).

**Surface.** For the same mass of any particular material, the combined surface area of a particle is inversely proportional to particle size. If the toxic properties of particles are determined by interactions occurring at the interface between particles and biological systems, then toxic response should correlate with the total surface area of particles. Indeed, it was observed in animal studies that the inflammatory response to inhaled TiO₂ particulates of different sizes, including those at the nanoscale size range, varied as a function of surface area (Oberdörster, 2000).

As particle size decreases, the fraction of atoms on the surface of the particle increases. This change becomes more pronounced for particles smaller than 100 nm in diameter with more than 1% of atoms on the surface and increases to 50% for 1 nm particles. Thus, surface characteristics, such as surface atomic and electronic structure and redox activity, become critical for nanoscale materials. Yet, toxic properties can be modulated by modifying the chemistry of the particle surface (Sayes et al., 2004). An example of this also comes from microbiology where surface chemistry plays a crucial role in the mechanism of viral infection. Receptor proteins expressed on the viral surface provide a mechanism for viral attachment to cellular membrane proteins of cells under attack. A slight modification of proteins expressed on the viral surface dramatically increases their virulence, or renders them innocuous (Wiley & Skehel, 1987).

**Shape.** One of the benefits of nanotechnology is the ability to control material structure with atomic precision. This control of materials on a nanoscale results in our ability to generate an immense number of engineered NPs with different shapes. Examples of the simplest engineered NPs are spheres, tubes, wires, rods, belts, and flakes. Examples of the more complex engineered NPs are tripods, flowers and brushes. Finally, the most complex NPs are three-dimensional structures such as multifunctional nanoscale particles like functionalized liposomes, virosomes and dendrimers.

Nanotubes and nanowires are shapes other than roughly spherical for which toxicological properties have been studied to some degree. Shape may be an important factor in toxicity as it has been shown that long carbon nanotubes cannot be engulfed by macrophages (Stone & Donaldson, 2006).

Properties of the core of nanoscale materials could also have effects on toxicological properties. For example, the electronic structure of the core could modulate reduction-oxidation type reactions on the particle surface. The chemical structure of the core could also become exposed during biodegradation and dissolution processes, and could exert toxicological effects distinct from those of the surface layer.

**Exposure and Dose Metrics**

Historically, a mass-based paradigm has been employed by industrial hygienists to assess worker exposure to airborne particulates. The exposure and dose metrics for engineered NPs in the workplace are now under active study because NPs have such little mass to measure. Since NPs have little mass, a new exposure and dose metrics may be needed. Currently, particle number and particle surface area are being studied as an exposure and dose metric.

An exposure and dose metric for engineered nanoscale materials, which have a range of either chemical compositions, or structures, or both, will depend on the mechanism of their toxicological and pharmacokinetic behavior. For example, poorly soluble low-toxicity particles, which interact with biological systems at the particle surface, can have their exposure and dose expressed as combined surface area. Thus, experimental studies in rodents and cell cultures have shown that the toxicity of nanoscale particles is greater than that of the same mass of larger particles of a similar chemical composition, and surface area correlates best with the observed toxicological responses (Oberdörster et al., 1994; Tran et al., 2000).

In addition to particle surface area, other particle characteristics may influence the toxicity, including solubility, shape, and surface chemistry (Oberdörster et al. 2005; Maynard & Kuempel, 2005). For nanoscale particles, which quickly disintegrate upon interaction with biological systems through dissolution or degradation (for example, water-soluble salts or quickly bio-degrading organic oligomeric particles), a mass-based metric could be sufficient to characterize exposure and dose. Using an analogy with asbestos and other mineral fibers for which fiber-count-based occupational exposure limits are used, an exposure and dose metric for fibers with diameters in the nanoscale range expressed as the number of fibers administered to the living system should be considered (NIOSH, 1997).

**Occupational Health Surveillance**

The unique physical and chemical properties of engineered nanomaterials, the increasing growth of nanotechnology in the workplace, and information suggesting that
engineered nanoscale materials may pose a health hazard to workers, all underscore the need for surveillance of exposed populations for adverse health effects. Existing medical and hazard surveillance mechanisms can be considered in designing site-specific occupational health surveillance programs for nanotechnology workers (Baker & Matte, 1994). It is likely that as the field of nanotechnology evolves over time, continual reassessment of potential hazards and exposures will be required to initiate and maintain an effective surveillance program. NIOSH is currently engaged in identifying the issues involved in occupational health surveillance for workers in nanotechnology research and development centers as well as those engaged in nanomanufacturing on the commercial level.

**Risk Assessment**

Risk assessment is a fundamental component of evaluating the occupational health risks of nanomaterials, and is the basis for effective risk management decisions (Herber et al., 2001). Quantitative risk assessment allows for a comparison between actual workplace exposure and a health risk-based occupational exposure limit (OEL). An example of quantitative risk assessment analysis for nanoscale particles can be found in the draft NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide (NIOSH, 2005). This document establishes a draft recommended exposure limit (REL) for nanoscale titanium dioxide (TiO$_2$) at 0.1 mg/m$^3$ as a timeweighted average concentration for up to 10 hr/day during a 40-hour work week, which is 15 times lower than the draft recommended exposure limit in the same document for macroscale TiO$_2$.

In the absence of adequate dose-response data for specific engineered nanoscale materials, qualitative risk assessment approaches can be used. Qualitative risk assessment can be based on comparisons between engineered nanoscale particles and incidental NPs, or to larger respirable particles, or fibers of similar chemical composition. An example of the qualitative risk assessment approach for nanoscale particles can be found in NIOSH’s web-based Approaches to Safe Nanotechnology: An Information Exchange with NIOSH, which we encourage readers to consult for current NIOSH risk management recommendations (NIOSH, 2006).

Given the paucity of data for a wide range of nanoscale materials, which are being used now in industry or in research laboratories, regulatory OELs, such as an OSHA mandatory permissible exposure limit (PEL), are unlikely to be promulgated for some time. Therefore, industry-based, or laboratory-based OELs could be established to facilitate development of a site-specific industrial hygiene program. Generic procedures to establish industry-based OELs were first developed by the pharmaceutical industry years ago and include the following steps: 1) evaluation of available animal, bioavailability and pharmacokinetic data; 2) supplemental studies to evaluate any health effects resulting from occupationally specific exposures, such as through dermal and inhalational exposures; 3) calculation of “no observed adverse effect level” or “the lower effective dose” in the benchmark dose method using the most sensitive occupationally relevant adverse effect; and 4) correction of this level for body weight, volume of air breathed during a typical workday (for inhalation route of exposures), and the uncertainty factor accounting for inter-individual variability and interspecies extrapolation (Agius, 1989; Naumann et al., 1996).

Physical factors affecting materials dispersion, such as volatility for liquid formulations and dustiness for dry formulations, also need to be considered when conducting risk assessments. While volatility can be more easily estimated using a well-established physical chemistry approach, evaluating the dustiness of powders can be more difficult. Dustiness can be measured using one of four general methods: 1) mechanical dispersion (vibration); 2) gravity dispersion (drop test); 3) gas dispersion (fluidized bed, for small samples (Boundy, 2006); and 4) re-suspension chamber (Hamelmann & Schmidt, 2004).

The biosafety community has often had to conduct risk assessment and risk management in the absence of OELs. For example, no OELs or “infectious doses for organisms” has been established by OSHA even though OSHA expressed some interest in doing so (Johnson, 2003). Currently, biosafety principles are based on assessing hazards of microorganisms according to their infectious capability, virulence and availability of effective treatments and preventative measures; and assigning microorganisms into one of four risk groups according to their hazards and routes of transmission (CDC & NIH, 2007).

Risk Group 1 includes agents not known to cause human disease, such as infectious canine hepatitis virus. Risk Group 2 includes indigenous moderate risk agents associated with human diseases of varying severity, such as salmonella. Risk Group 3 includes indigenous or exotic agents associated with human disease and with a low potential for human-to-human transmission. Risk Group 4 includes dangerous or exotic agents of a life-threatening nature, which may be transmitted via aerosol route and for which there is no available vaccine or therapy, such as hemorrhagic fever viruses. Similarly, binning of engineered nanoscale materials according to their anticipated degree of hazard is under consideration within a “control banding” approach to nanotechnology. In general, control banding means a process in which a single control technology (such as general ventilation or containment) is applied to one range or band of exposures to a chemical (such as 1-10 mg/m$^3$) that falls within a given hazard group (such as skin and eye irritants, or severely irritating and corrosive). The most developed model for control banding in occupational health has been established by the Health and Safety Executive (HSE) of the United Kingdom (HSE, 2007).
Risk Management

Risk management programs aimed at minimizing the risk of exposure are routinely implemented in the workplace, including research laboratories and health care facilities. Important elements of a risk management program include the establishment of guidelines for installing and evaluating engineering controls such as, exhaust ventilation, education and training of workers in the proper handling of nanomaterials (good work practices), and the development of procedures for selecting and using personal protective equipment (PPE), such as clothing, gloves, and respirators (NIOSH, 2006).

As noted above, the health care and pharmaceutical industries have long recognized the need for controlling occupational exposures to biologically active entities such as pharmaceutical and infectious agents. Biologically active ingredients often are not sufficiently characterized toxicologically to establish health-based OELs. To overcome this deficiency hindering the establishment of rigorous industrial hygiene practices, an alternative approach, based on semi-quantitative criteria for assessing health risks of compounds and effectiveness of control techniques, has been developed and employed by the pharmaceutical industry (Olson et al., 1997; Heidel, 2001).

In this approach known as “exposure banding,” substances are assigned into one of five occupational hazard bands using available toxicological information. Each band corresponds to a set of controls necessary to provide protection for workers. The controls can range from open-air handling for low hazard substances to the use of ventilated enclosures and glove boxes for working with high hazards substances. Each band can be further divided into inhalation and dermal (Goede et al., 2003) exposure classes, which are then assigned a set of controls necessary to provide protection for workers.

Similarly, risk from biological hazards is reduced with combinations of laboratory practices and techniques, safety equipment, and laboratory facilities prescribed to four biosafety levels (CDC & NIH, 2007). Biosafety levels correlate, but do not equate with Risk Groups. In deciding which biosafety level is most appropriate for a specific site, the hazard of an agent expressed as an agent’s Risk Group and exposure potential related to the mode of transmission, procedural protocols, and experience of staff are assessed. Biosafety Level 1 (BSL-1) represents the most basic level of containment that relies on standard microbiological practices with no special primary or secondary barriers. In BSL-2, the primary hazards to workers come from accidental percutaneous, or mucous membrane exposures, or ingestion of infectious materials. Biosafety cabinets (BSC), splash shields, face protection, gloves, and lab coats are used as primary barriers. In BSL-3 all laboratory manipulations are performed in enclosed equipment, such as biosafety cabinets, and secondary barriers include ventilation requirements to minimize release into the environment. For infectious agents handled under BSL-4, primary hazards come from respiratory, mucous membrane, or broken skin exposures. Complete isolation of workers is achieved with a Class III BSC and/or a full-body, air-supplied positive pressure personnel suit. Secondary barriers include complete isolation with specialized ventilation requirements and waste management systems to prevent the release of viable agents into the environment.

In the case of potential exposures to biological agents, including nanoscale agents outside controlled environments, NIOSH Interim Recommendations for the Selection and Use of Protective Clothing and Respirators Against Biological Agents (NIOSH, 2001) suggest using a half-mask, or full facepiece air-purifying respirators with particulate filter efficiencies of P100 for hazards such as hantavirus as a minimum level of protection. Self-contained breathing apparatus (SCBAs) respirators, with a full facepiece operated in positive pressure mode, are recommended for use when hazards and airborne concentrations are either unknown, or expected to be high. Protective clothing, including gloves, lab coats, and booties also provide protection against dermal exposures to biological agents.

NIOSH’s Approaches to Safe Nanotechnology describes current NIOSH recommendations for control measures to reduce exposures to nanoscale engineered materials in general occupational setting (NIOSH, 2006). In general, control techniques such as source enclosure (isolating the generation source from the worker), and local exhaust ventilation systems are expected to be effective for capturing airborne engineered nanoscale particles based on what is known of nanoscale particle motion and behavior in air (Seinfeld & Pandis, 1998; Hinds, 1999). Current knowledge also indicates that a well-designed exhaust ventilation system with a high-efficiency particulate air (HEPA) filter should effectively remove NPs (Hinds, 1999; NIOSH, 2003). Filters are tested using particles that have the lowest probability of being captured, typically around 300 nm in diameter. It is expected that the collection efficiencies for smaller particles should exceed the measured collection efficiency at this particle diameter (Lee & Liu, 1982; Pui & Kim, 2006). Similarly, it is expected that NIOSH certified respirators can provide the expected levels of protection (NIOSH, 2004).

Conclusion

Current approaches to risk management for engineered nanomaterials, such as engineering control, administrative control, PPE and health surveillance, parallels approaches already in practice in occupational health and biosafety. Further research and investigation is needed to evaluate the effectiveness of these approaches across the spectrum of engineered nanomaterials being used and generated in laboratories and industry.
NIOSH’s Nanotechnology Research Center aims to identify the risk implications of nanotechnology for worker health, and to devise ways to protect workers from any identified adverse health effects of working with nanomaterials by developing novel approaches to risk assessment and management. Examples of NIOSH’s activities include the following: an inter-disciplinary field team partnering with nano-enabled research and development labs and manufacturing sites to assess exposures and effectiveness of risk management practices; dynamic web-based NIOSH recommendations that are regularly updated to reflect new knowledge obtained through research and surveillance; multiple projects to assess the pulmonary, cardiovascular, dermal and neural effects of engineered NPs; development of risk assessment models and exposure monitoring techniques; and active participation in the development of governmental and non-governmental programs and standards both nationally and internationally. Close collaborations between all nanotechnology stakeholders—academia, government, labor, industry, practitioners and the public—is necessary to ensure that the potential of nanotechnology to improve level of life is realized at the same time that occupational health concerns are effectively addressed. With nanotechnology, we still have a chance to do it right the first time.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Abstract

Due to the size and importance of agriculture to many countries, it is vital to safety contain highly virulent animal pathogens while conducting research or diagnostics involving those pathogens. Most agricultural pathogens can be studied safely in the laboratory or vivarium at Biosafety Level (BSL) -2 or -3, or Animal Biosafety Level (ABSL) -2 or -3. However, when animals are infected with certain highly virulent agricultural pathogens and there is no alternative other than loose-housing in a room, special requirements for containment are needed. This standard has become known as Biosafety Level 3 Agriculture (BSL-3-Ag) in North America and constitutes a special set of facility, operational and personnel requirements. In order to determine which biosafety level is appropriate for the containment of the animal pathogen being studied, an on-site risk assessment must be conducted, which takes into account many different factors. In addition, the final approval to work with a particular agricultural pathogen is often provided by the local and/or national government and may require further assessments.

Introduction

This document intends to provide recommendations for biocontainment levels required to work with agriculture pathogens or agents that specifically infect animal species traditionally used in agriculture. The scope of this paper does not cover other areas of agricultural risk, which includes foreign diseases of crops, biocontrol activities, and work involving arthropods and genetically engineered agricultural products. Information on these subjects can be found elsewhere (Scott, 2005; Delsosse, 2005; Chapman & Burke, 2006; Traynor, et al., 2001). This document is not only relevant to traditional livestock species, which include cattle, pigs, sheep, goats, horses, and a wide variety of avian species, but also to wildlife when appropriate.

Globally there are a large number of pathogens, including parasites, bacteria, viruses, mycoplasma and prions that infect domestic agriculture species and wildlife. There is a wide range of geographic presence of these pathogens that determines a country’s animal health status, at least in part. Many nations have worked diligently for decades to eradicate the most economically significant animal diseases from their national herds. This has provided those countries with better economic animal production and favored trade status. Many of these countries have a continued interest in studying these now non-endemic, highly infectious agents both in vivo and in vitro. One of the goals of such research is to ensure availability of adequate diagnostics, vaccines and other tools that could be utilized during a potential outbreak, either naturally occurring, or as a result of agroterrorism. Regardless of how a serious foreign animal disease (FAD) is introduced into a country’s animal production system, it is expected that severe losses to the economy would occur. Therefore, this document intends to provide some recommendations for appropriate biocontainment, and practices to conduct studies of significant agricultural pathogens in both laboratory and vivarium settings.

Commercial Agriculture

Agriculture is big business. In the United States, it is estimated that animal agriculture constitutes 13% of the gross national product; 17% of all employment in the U.S. is either directly or indirectly working in agriculture. In 2006, there were approximately 88 million beef cattle, 9.2 million dairy cattle and 9.7 billion poultry in the U.S. (National Agriculture Statistics, 2006). When animal health problems occur and the agriculture economy is affected it impacts the entire U.S. economy. Since it is possible to start a widespread outbreak from a single source, preventing an accidental release of a highly infectious organism from a biocontainment facility is of the utmost importance. Most animals in the U.S. are not vaccinated against many foreign animal diseases (FADs) and are very susceptible to infection from these agents. If a highly infectious agent is introduced into a modern agricultural system, models have shown that the pathogen can rapidly move from one farm to another via the infected animals. Intensive, modern agricultural practices promote high-density livestock populations, which are bred and reared in close proximity to one another. The outbreak of a contagious FAD at one of these facilities would be very difficult to contain, especially if the disease is airborne and shed in large quantities.

Problems with contagious disease outbreaks are exacerbated by the distant and rapid dissemination of animals from farm-to-farm, or in farm-to-market distribution nodes. In many cases, such as in the cattle industry, dairy and beef animals are born in one location, raised in another location and live their production life in yet another location. For example, a representative survey of U.S. barn auctions revealed that between 20 and 30 percent of cattle were regularly consigned to nonslaughter

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Chapman & Burke, 2006; Traynor, et al., 2001)
destinations at least 30 miles from their original point of purchase, and in many cases had crossed several states within 36 to 48 hours of leaving the sales yard (Chalk, 2004). Because farms are tightly interconnected with other farms and distribution nodes, infectious agents can move extremely rapidly across the United States. Thus, small local outbreaks can rapidly become large national outbreaks. Some estimates have determined that an outbreak of Foot-and-Mouth Disease (FMD) in the U.S. would cost $33 billion to eradicate (Lautner & Meyer, 2003). However, that may be an underestimate based upon outbreak costs in other countries. FMD in the UK, which started in 2001, cost the country $15 billion; Classical Swine Fever (CSF) in the Netherlands in 1997 cost $3.4 billion; highly pathogenic avian influenza (HPAI) in the U.S. in 1983 cost $349 million; Exotic Newcastle disease, in California in 2003, cost $360 million to eradicate. Many of these costs are due to the effect a disease outbreak has on export trade. Export of agricultural products is one of the few areas where the U.S. has a positive trade balance. World trade has dramatically increased in the last 20 years ($2.4 trillion in 1980 to $8.0 trillion in 2000). U.S. exports have been continuously climbing with $103 billion in exports and 860,000 jobs related to exports. All of those gains could be jeopardized if a serious disease outbreak involving a FAD, or a disease that has been previously eradicated occurred among livestock. Other economic impacts would include: loss of production; losses to related industries such as transportation; the direct costs of outbreak control; and indirect costs to non-agricultural industries, such as tourism due to restriction of movement in and out of impacted areas.

Animal/Livestock Agents of Agricultural Concern

In the U.S., the United States Department of Agriculture (USDA) generally responds to outbreaks of highly pathogenic organisms with a test and slaughter policy. In order to prepare for these outbreaks, pathogenesis studies of the organism are required to develop better diagnostic tools and establish effective countermeasures. There is a need for laboratories where these pathogens are studied, both in vitro and in vivo, to employ appropriate biocontainment. These laboratories typically require levels of biocontainment beyond what is required for endemic pathogens to ensure that these FADs stay confined to the research environment.

There are many pathogens (Table 1) that infect agricultural species that could cause economic problems to a region, state or nation. Many of these pathogens are still widely distributed around the world and continue to cause agriculture production losses. It has been difficult to devise a single global ranking for agricultural pathogens due to the factors of economic impact and disease status between countries and regions within countries (Rusk, 2000). A global risk assessment guideline for diseases of livestock and crops is desperately needed. The U.S. and other developed countries have invested significant resources, both human and financial to eliminate many of the most economically damaging disease agents from their national herds. For many of these agents, there is no treatment or vaccine; therefore, the most efficient and rapid method of removing the agent if an outbreak should occur is to remove the susceptible hosts, thus necessitating effective biocontainment when studies are conducted within a laboratory or vivarium.

Risk Assessment

Risk analysis is a “body of knowledge” (methodology) that evaluates and derives a probability of an adverse effect of an agent (chemical, physical or other), industrial process, technology, or other technology (Molak, 1997). The National Academy of Sciences (1983) identified four common elements in risk analysis:

1. Hazard (agent) identification
2. Dose response
3. Exposure analysis
4. Risk characterization

Risk assessment is “risk analysis applied in a particular situation” (Molak, 1997). Many institutions and organizations throughout the world must consider the risks presented by proposed research with agricultural pathogens, and make decisions regarding the placement of these pathogens into proper biocontainment and biosafety categories. In the U.S., the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) published guidelines that are universally accepted as the basic standard for biosafety (Centers for Disease Control and Prevention and National Institutes of Health, 2007). Although this system is appropriate and accepted for agents of human and zoonotic diseases, it cannot be universally applied to biocontainment for pathogens that infect only livestock (Rusk, 2000). In the development of risk assessment and management guidelines for agriculture, it must be recognized that the rationale for agricultural standards will differ from those for human public health standards and those for worker protection. Risk management for agriculture research is based on the potential economic impact on animal and plant morbidity and mortality, and the trade implications of disease.

In conducting a risk assessment, agricultural regulatory agencies, such as the United States Department of Agriculture-Animal and Plant Health Inspection Service (USDA-APHIS), will consider a wide variety of factors when determining what level of biocontainment and biosafety is appropriate, and what additional enhancements may be required for research involving livestock pathogens. Just a few of these include the following:

1. Is the agent endemic, or foreign to the region?
2. What is known regarding the morbidity and mortality caused by the agent?
3. Are there effective prophylaxes, treatments or vaccines available?
4. What are the shedding patterns of the agent in relevant species?
5. Are there active control or eradication programs for the disease?
6. Knowledge of environmental stability, quantity and concentration of the agent.
7. How will the agents be used in animals (large or small), or in the laboratory?
8. What is the host range of the agent, and is there ongoing surveillance testing?

In addition to the biological factors of the agent, consideration will also be given to the people using the agent such as their level of experience and knowledge, practices used, experimental design and protocols, standard operating procedures, and facility design and management.

Risk management strategies identify and implement methods to reduce risk to an acceptable level. To mitigate risk, biosafety professionals can use a combination of practices and techniques, along with safety equipment and facilities working in concert to enable agricultural pathogens to be studied safely (Rusk, 2000). A risk assessor or manager has additional risk management options available to them for controlling an agricultural hazard that do not represent a risk to human researchers. In an agricultural setting, consideration for seasonal separation, climatic and geographic factors, and host and/or vector availability outside the research environment can all play a role in determining the appropriate biocontainment level. For example, a FAD livestock pathogen only transmitted by a specific arthropod vector may typically require a high biocontainment level (BSL-3-Ag) when viable vectors and hosts were present in the outside environment. However, this pathogen could potentially be studied at a lower containment level in situations where the vector or potential hosts are absent (e.g., where there is climatic, seasonal, or geographic separation).

In addition to describing various biocontainment standards appropriate for working with agricultural pathogens, this document also describes the facility parameters and work practices that have come to be known as BSL-3-Ag. BSL-3-Ag is unique to agriculture because of the necessity to protect the environment from an eco-

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### Table 1

Agents of greatest concern to the health and productivity of agricultural animals.

<table>
<thead>
<tr>
<th>Agent</th>
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<tbody>
<tr>
<td>African horse sickness virus</td>
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<tr>
<td>African swine fever virus</td>
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<td>Akabane virus</td>
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<tr>
<td>Avian influenza virus (highly pathogenic)</td>
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<tr>
<td><em>Bacillus anthracis</em></td>
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<td>Besnoitia besnoiti</td>
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<tr>
<td>Bluetongue virus (exotic)</td>
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<td>Borna disease virus</td>
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<tr>
<td>Bovine infectious petechial fever agent</td>
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<tr>
<td>Bovine spongiform encephalopathy</td>
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<tr>
<td><em>Brucella abortus</em></td>
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<td><em>Brucella melitensis</em></td>
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<td><em>Brucella suis</em></td>
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<tr>
<td><em>Burkholderia mallei</em> (Pseudomonas mallei - Glanders)</td>
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<tr>
<td><em>Burkholderia pseudomallei</em></td>
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<tr>
<td>Camelpox virus</td>
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<tr>
<td>Classical swine fever virus</td>
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<tr>
<td>Coccidiodes immitis</td>
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<tr>
<td><em>Coxiella burnetii</em> (Q fever)</td>
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<tr>
<td>Ephemeral fever virus fever agent</td>
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<tr>
<td>Eastern equine encephalitis virus</td>
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<td>Foot and mouth disease virus</td>
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<tr>
<td>Francisella tularensis</td>
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<tr>
<td>Goat pox virus</td>
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<td>Hendra virus</td>
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<tr>
<td><em>Histoplasma (Zymonema) farcinosum</em></td>
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<td>Infectious salmon anemia virus</td>
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<td>Japanese encephalitis virus</td>
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<tr>
<td>Louping ill virus</td>
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<td>Lumpy skin disease virus</td>
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<tr>
<td>Malignant catarrhal fever virus (exotic strains or alcelaphine herpesvirus type 1)</td>
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<tr>
<td>Menangle virus</td>
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<tr>
<td>Mycobacterium bovis</td>
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<tr>
<td><em>Mycoplasma agalactiae</em></td>
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<td><em>Mycoplasma capricolum</em></td>
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<tr>
<td><em>Mycoplasma mycoides</em> (small colony type)</td>
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<tr>
<td>Nairobi sheep disease virus (Ganjam virus)</td>
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<td>Newcastle disease virus (velogenic strains)</td>
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<td>Nipah virus</td>
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<tr>
<td>Peste des petits ruminants virus (plague of small ruminants)</td>
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<td>Rift Valley fever virus</td>
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<tr>
<td>Rinderpest virus</td>
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<tr>
<td>Sheep pox virus</td>
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<tr>
<td>Spring Viremia of Carp virus</td>
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<tr>
<td>Swine vesicular disease virus</td>
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<tr>
<td>Teschen disease virus</td>
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<tr>
<td>Theileria annulata</td>
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<tr>
<td>Theileria bovis</td>
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<tr>
<td>Theileria hirci</td>
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<td>Theileria lawrencei</td>
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<tr>
<td><em>Trypanosoma brucei</em></td>
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<tr>
<td><em>Trypanosoma congoense</em></td>
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<tr>
<td><em>Trypanosoma equiperdum</em> (dourine)</td>
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<tr>
<td><em>Trypanosoma evansi</em></td>
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<tr>
<td><em>Trypanosoma vivax</em></td>
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<tr>
<td>Venezuelan equine encephalomyelitis virus</td>
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<td>Vesicular exanthema virus</td>
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<tr>
<td>Vesicular stomatitis virus (field strains, exotic)</td>
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<td>Viral hemorrhagic disease of rabbits virus</td>
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<td>Wesselsbron disease virus</td>
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nomic, high-risk pathogen in a situation where studies are conducted employing large agricultural animals, or other similar situations in which the facility barriers now serve as primary containment. This document also describes some of the enhancements beyond BSL-3 that may be required by the USDA-APHIS when working in the laboratory or vivarium with veterinary agents of concern. The document provides guidance to researchers working with veterinary agents of concern, and is not regulatory, or meant to describe national or international policy. Conditions for approval to work with specific agricultural agents are provided at the time USDA-APHIS or the veterinary authority of the country permits a location to work with an agent.

**Containment Standards Appropriate for Working with Agriculture Pathogens**

**Biosafety Level**

A combination of work practices and physical containment requirements (facility and safety equipment) are designed to reduce the risk of laboratory infection when working with biohazardous material. The degree of protection recommended is proportional to the risk associated with an agent and the proposed research operations. When studying agriculture pathogens in the laboratory there are 4 proposed biosafety levels that can be used. When studying agriculture pathogens in the vivarium, there are 4 proposed biosafety levels that can be used with the additional criteria of BSL-3-Ag reserved for studying high consequence pathogens in loose-housed animals where the room becomes the primary containment. The biosafety levels described in the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) specify many of the containment features that could be utilized as a basis for agricultural research. However, the authors re-emphasize the difference in risk assessment criteria between public health and worker protection and agricultural containment requirements. Others have also described similar biocontainment principles and practices (Barbeito et al., 1995; Best, 1996).

**Proposed Laboratory Biosafety Levels**

**BSL-1.** Facility and practices appropriate for work with well-characterized, low-risk agents not known to cause disease in healthy animals that represent no potential economic loss to agricultural industries. No specialized practices other than good microbiological technique are utilized. Facilities should be easily cleanable, have a sink for hand washing, and conform to the facility requirements described in the BMBL for BSL-1. These laboratories are typical of undergraduate, or secondary education teaching laboratories.

**BSL-2.** Facility, safety equipment and practices appropriate for agents of moderate potential hazard to animals or agriculture that are generally endemic, cause illness of varying degree, and are typically treatable or preventable. Most research and diagnostic laboratories that work with food-borne pathogens and domestic diseases are designed to perform work at this level.

**BSL-3.** Facility, safety equipment and practices that are applicable to clinical, diagnostic, research, or production facilities in which work is done with indigenous or exotic agents with a potential for transmission, and which may cause serious and potentially lethal infections in animals, or grave economic consequences to agriculture if released. Laboratory facility and practices include inward directional airflow, separation from non-laboratory areas, special laboratory protective clothing, and decontamination of laboratory waste. For in vitro work with some highly infectious agriculture agents, BSL-3 may be modified further with enhancements specifically designed to protect the environment such as high-efficiency particulate air (HEPA) filtration of supply and exhaust air, laboratory liquid effluent/sewage decontamination, personnel exit showers, and facility integrity testing, if required by the risk assessment for the agent and planned manipulations.

**BSL-4.** Facility, safety equipment and practices appropriate for research on dangerous and exotic agents that pose a high individual risk of human life-threatening disease which may be transmitted via the aerosol route and for which there is no available vaccine or treatment. While there is no BSL-4 requirement solely for agricultural agents, two viruses have recently been discovered that are lethal for agricultural species and for humans (Nipah and Hendra viruses) and for which there are no vaccines. These agents can only be manipulated at laboratories having BSL-4 capability. At present, the U.S. does not have this containment capability for large animals. This underscores the need to establish an ABSL-4 laboratory in the U.S. that is designed to accommodate large agricultural species. Currently, fewer than 20 viruses are designated for use at BSL-4.

**Proposed Vivarium Biosafety Levels**

**ABSL-1.** Facility and practices appropriate for work with well-characterized, low-risk agents not known to cause disease in healthy animals. No specialized practices other than good microbiological technique are utilized. These facilities are typical of university or industry research farms.

**ABSL-2.** Facility, safety equipment and practices, appropriate for agents of moderate potential hazard to animals or agriculture that are generally endemic, cause illness of varying degrees, and are typically treatable or preventable. Most research and diagnostic vivariums that work with food-borne pathogens and domestic diseases are designed to perform work at this level.

**ABSL-3.** Facility, safety equipment and practices applicable to clinical, diagnostic, research, or production facilities in which work is done with indigenous or exotic agents with a potential for transmission, and which may
cause serious and potentially lethal infections in animals, or grave economic consequences to agriculture if released. Vivarium facility and practices include inward directional airflow, separation from uninfected animal areas, special laboratory protective clothing, and decontamination of laboratory waste. For in vivo work with some highly infectious agriculture agents, ABSL-3 may be modified further with enhancements specifically designed to protect the environment such as placing animals in isolation containers (isolets or flexible film isolators) with HEPA filtration of supply and exhaust air, sewage decontamination, personnel exit showers, and facility integrity testing (pressure decay test).

**BSL-3-Ag.** The USDA Agricultural Research Service (ARS) has defined enhanced ABSL-3 facilities, safety equipment and practices particular to agriculture research where the facility barriers, usually considered secondary barriers, now act as primary barriers. This standard is used when large animals such as cows, pigs, bison and deer, are infected with high consequence agricultural pathogens and cannot be placed inside any other animal isolation device. BSL-3-Ag facilities utilize the containment features of the standard ABSL-3 facility (as defined in the BMBL) as a starting point, with a number of enhancements specifically designed to protect the environment such as HEPA filtration of supply and exhaust air, sewage decontamination, personnel exit showers, and facility integrity testing (pressure decay test). FMD, CSF, and HPAI are representative of agricultural agents may be assigned to this biosafety level.

**ABSL-4.** Facility, safety equipment and practices appropriate for research on dangerous and exotic zoonotic agents that pose a high individual risk of human life-threatening disease, which may be transmitted via the aerosol route, and for which there is no available vaccine, or treatment. This standard would have all of the features of a BSL-3-Ag facility with added worker protection. While there is no ABSL-4 requirement solely for agricultural agents, recently two viruses have been discovered that are lethal for agricultural species and for humans (Nipah and Hendra viruses) for which there are no vaccines. These can only be manipulated in vivaria having ABSL-4 capability.

**Facility Design and Standard Operating Procedure Enhancements for Laboratories and Small Animal Facilities Working with High Consequence Foreign Animal Diseases**

There are circumstances where certain agents that typically would be required to utilize a BSL-3-Ag facility for research involving large animals may be studied in an enhanced BSL-3 laboratory, or an enhanced ABSL-3 vivaria, for work with small animals in which primary containment devices can be utilized. In these situations, the facility no longer serves as the primary barrier as it does with the large animal rooms. The design and testing requirements for BSL-3-enhanced laboratory areas should reflect the difference between the two situations without compromising the environmental protection that is required when working with these agents. Therefore, when manipulating high consequence livestock pathogens in the laboratory, or small animal facility, facility design and work procedures must meet the requirements of ABSL-3 with additional enhancements unique to agriculture. In addition to meeting the basic ABSL-3 requirements, the facility should have personnel enter and exit through a clothing change and shower room, have a double-door autoclave and/or fumigation chamber, HEPA-filtered supply and exhaust air, and a liquid effluent decontamination system. Surfaces must be smooth to support surface wipe-down decontamination, all penetrations should be sealed, and the room capable of containing a fumigant in instances where gaseous decontamination is required. Since all work with infectious material is conducted within primary containment, there is no requirement for pressure decay testing.

**Laboratory Facilities and Small Animal Vivaria**

Potential enhancements beyond BSL-3 for containment of agriculture pathogens in the laboratory are agent and site dependent and may include the following:

1. Personnel change and shower rooms that provide for the separation of street clothing from laboratory clothing and that control access to the containment spaces.
2. Access doors to these facilities that are self closing and lockable.
3. Supplies, materials, and equipment enter the BSL-3 enhanced space only through an airlock, fumigation chamber, or an interlocked double-door autoclave.
4. Double-door autoclaves engineered with bioseals should be provided to decontaminate laboratory waste passing out of the containment area.
5. Dedicated, single pass, directional, and pressure gradient ventilation systems must be used.
6. Supply and exhaust air, to and from the containment space is HEPA filtered, with special electrical interlocks to prevent positive pressurization during electrical or mechanical breakdowns. Alternatively, the supply air may not be HEPA filtered but equipped with a fast-acting bioseal damper which is interlocked with the exhaust fan to ensure that potentially contaminated air is not released through the air intake during an HVAC failure.
7. Liquid effluents (sinks, toilets, floor drains, showers) from BSL-3 enhanced areas may be collected and decontaminated by a method validated to inactivate the agent being used (a central liquid waste sterilization system is recommended) before disposal into the sanitary sewer system. The treatment requirement will be determined by a site-specific, agent-specific risk assessment.
8. Each BSL-3 enhanced containment space shall have its interior surfaces (walls, floors, and ceilings) and penetrations sealed to create a functional area capable of being validated as airtight. All ductwork within containment serving BSL-3 enhanced spaces shall be airtight (pressure tested—consult your facility engineer for testing and certification details). If Biological Safety Cabinets are installed, they must be installed where their operations are not adversely affected by air circulation and personnel traffic.

**Facility Design and Standard Operating Procedure Enhancements for BSL-3 Agriculture**

The BSL-3-Ag facility can be a separate building, but more often it is an isolated zone contained within a facility operating at a lower biosafety level, usually BSL-3. This isolated zone has strictly controlled access, special physical security measures, and functions with the "box within a box" principle. All BSL-3-Ag facilities employing animals that cannot be readily housed in primary containment devices require the same features as for an animal ABSL-3 facility with the following enhancements typical of BSL-4 facilities (Heckert & Kozlovac, 2006):

1. Personnel change and shower rooms that provide for the separation of laboratory clothing from animal facility clothing, and that control access to the containment spaces.
2. Access doors to these facilities are self closing and lockable.
3. Supplies, materials and equipment enter the BSL-3-Ag space only through an airlock, fumigation chamber, or shower.
4. Double-door autoclaves engineered with bioseals are provided to decontaminate laboratory waste passing out of the containment area.
5. Dedicated, single pass, directional, and pressure gradient ventilation systems must be used.
6. Supply and exhaust air, to and from the containment space is HEPA-filtered with special electrical interlocks to prevent positive pressurization during electrical or mechanical breakdowns. Alternatively, the supply air may not be HEPA filtered, but must be equipped with a fast-acting, bioseal damper which is interlocked with the exhaust fan to ensure that potentially contaminated air is not released through the air intake during an HVAC failure.
7. Liquid effluents from BSL-3-Ag areas must be collected and decontaminated in a central liquid waste sterilization system before disposal into the sanitary sewer system.
8. Each BSL-3-Ag containment space shall have its interior surfaces (walls, floors, ceilings) and penetrations sealed to create a functional area capable of being validated as tightly sealed (airtight). It is recommended that the validation process includes a pressure decay test (for new construction only). Information on how to conduct a pressure decay test may be found within Appendix 9B of the ARS Facilities Design Standard (Policy and Procedure 242.1M-ARS).
9. All ductwork within containment serving BSL-3-Ag spaces should be airtight (pressure tested—consult your facility engineer for testing and validation details).
10. The hinges and latch, or knob areas of all passage doors shall be sealed to meet pressure decay validation requirements (pressure decay test).
11. All airlock doors shall have air inflated, or compressible gaskets.
12. Animal restraining devices shall be provided in large animal rooms.
13. Necropsy rooms shall be sized and equipped to accommodate large farm animals.
14. Pathological incinerators or other approved means must be provided for the safe disposal of the large carcasses of infected animals.
15. HEPA filters or the equivalent must be installed on all atmospheric vents serving plumbing traps as near as possible to the point of use or the service cock of central or local vacuum systems, and on the return lines of compressed air systems.

**Conclusions**

Many of the practices and policies described in the U.S. CDC/NIH publication entitled *Biosafety in Microbiological and Biomedical Laboratories* can be applied to work with agricultural pathogens. However, it must be noted that the risk assessment criteria for agriculture are different than those for public health and worker safety. Risk management strategies for work involving agriculture pathogens must focus on biocontainment and environmental protection in addition to worker protection, since the primary concern is the potential economic impact of the morbidity and mortality on agricultural species, and the international trade implications of a disease outbreak. Those pathogens with which work is being done that have the highest economic consequence to the animal health status of the country require the highest level of biocontainment. For most agriculture pathogens, BSL-3 or BSL-2 and ABSL-2 or ABSL-3 standards are acceptable and achieve an appropriate level of biocontainment. However, for some agriculture pathogens, there is a special concern for reducing the risk of environmental exposure or escape from the facility. Therefore, ABSL-3 facility standards with enhancements to safety equipment and practices particular for agriculture research (i.e., infectious disease work with large agricultural animals) where the facility barriers (usually considered secondary barriers) now act as primary barriers have been established (USDA Agriculture Research Service Manual 242.1, CDC/NIH BMBL 5th edition; Heckert & Kozlovac, 2006; Best, 1996). The U.S. standard, referred
to as BSL-3-Ag, utilizes the containment features of the standard ABSL-3 facility (as defined in the BMBL) as a starting point, and includes the majority of enhancements typically assigned to ABSL-4. These enhancements are provided specifically to protect the environment, and include HEPA filtration of supply and exhaust air, decontamination of liquid effluent, decontamination of solid wastes, including carcass disposal, personnel exit showers, and facility integrity testing (pressure decay test). This type of facility is appropriate for non-endemic pathogens causing serious livestock, or poultry disease that are readily transmitted to agricultural species and wildlife.

Acknowledgements

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References


Minimization of the Risks Posed by Dual-Use Research: A Structured Literature Review

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Abstract

Introduction: In a post-9/11 world, the potential risks associated with biodefense research are great. The dual-use dilemma concerns the ability of legitimate biomedical research intended to be used for societal good, to instead be subverted for the development of biological weapons causing a threat to the population. The objective of this study was to review the current life sciences literature in order to identify options to minimize the risks associated with dual-use research.

Methods: The MEDLINE database was searched for studies concerning the ethics of biodefense, or the dual-use dilemma. Ten articles met all inclusion criteria and were thoroughly reviewed and analyzed.

Results: The most commonly suggested strategy for minimizing the potential harm caused by scientific research was self-regulation within the scientific community followed by increased security within the scientific community, international cooperation, and finally, increased biodefense education for professionals. One article suggested that decreases in forced security would minimize the risk of the dual-use of bioterrorism through increased open scientific scrutiny and self-regulation within the community. Another article argued for more clarity in guidelines to define the type of research that would require increased security. Strategies were not mutually exclusive with many articles offering combination approaches to minimize dual-use risks.

Conclusions: To offer the best protection against terrorist use of dual-use research from a biological sciences perspective, many of the proposed measures need to be undertaken simultaneously.

Introduction

On September 11, 2001, the United States experienced the largest domestic terrorist attack in its history. A few weeks later, B. anthracis spores were disseminated through the postal system. Since then, the United States government has reevaluated the threats posed by terrorism, determined that bioterrorism is a substantial threat to its people (Federal Bureau of Investigation Strategic Plan, 2004-2009), and spent substantial resources to prepare the nation against a future biological terrorist attack. In 2006, the U.S. government spent approximately $5.1 billion on civilian biodefense (Schuler, 2005), a dramatic increase even from 2001, when funding for biodefense was only $295 million (Lam, Franco, & Schuler, 2006). The budgeted U.S. government funding for civilian biodefense in the fiscal year 2007 is $5.2 billion, an increase of more than 1,700% over biodefense spending in 2001 (Lam, Franco, & Schuler, 2006) Despite such a clear increase in biodefense spending by the government, many scientists and ethicists have suggested that such research may be unethical for a variety of reasons (King, 2005; Atlas, 2005).

Many ethical issues have been raised regarding biodefense, including the use of scarce public health resources for defense against an unlikely threat, the threat classified scientific research poses to national security, safety and ethicality of actual experiments, and how to determine the best approach when responding to an act of bioterrorism (King, 2005; Atlas, 2005). The ethical issue that seems most prominent at the moment is that of the “dual-use dilemma.” Traditionally, the term “dual-use” has referred to research that has both civilian and military applications, but recent developments in the life sciences have expanded the dimensions of the “dual-use” term to include possible offensive or hostile purposes (Atlas & Dando, 2006). In the life sciences literature today, the dual-use dilemma concerns the ability of legitimate biomedical research intended to be used for societal good to be used for the development of biological weapons causing a threat to the population (King, 2005; Kelley, 2006). Such a threat may involve researchers inadvertently creating a more virulent strain of an organism while searching for a mechanism to disarm it or trying to create less virulent strains. It is also possible for researchers to make a nonpathogenic organism virulent. Additionally, research that creates a strain of organism that is resistant to antibiotics or antivirals, or to develop a strain that evades diagnosis is seen as having dual-use potential (Atlas & Dando, 2006). Similarly, research in aerosol technology, commonly conducted when developing therapeutic drug delivery systems, could be utilized to weaponize pathogens.

In one controversial study resulting in potential dual-use implications, researchers published the complete methodology and results for synthesizing an artificial poliovirus with the biochemical and pathogenic characteristics of the actual poliovirus. This publication raised serious concerns that these scientists were offering potential blueprints to terrorists for creating similar viruses (Cello & Wimmer, 2002). In 2005, two controversial studies published the full genome sequence of the 1918 flu virus,
which killed an estimated 50 million people worldwide (Tumpey et al., 2005; Taubenberger et al., 2005; Sharp, 2005). Although the public availability of the full genome sequence can lead to the development of new therapies and vaccine, it could also be used by terrorists to start another pandemic. In the week prior to publication of this groundbreaking work, the U.S. National Science Advisory Board for Biosecurity (NSABB) called an emergency meeting to consider the risks, but came to the conclusion that the benefits outweighed the risks and the publication went forward as scheduled (Von Bubnoff, 2005).

The purpose of this paper is to review the current life science literature on the ethics of biodefense with the goal of identifying salient issues in the ethics of the dual-use dilemma and methods for minimizing the harm that could potentially be caused by biological research. As the purpose of this paper was to focus on the relevant issues from the perspective of the life sciences, policy publications were not considered during the review process.

Methods

In order to identify relevant articles, a search of the MEDLINE database was conducted for key words including: "biodefense," "biowarfare," "biosecurity," "biotechnology," "biological weapons," "bioethics," "biodestressing," and "dual-use," both alone and in combinations. Studies were selected if their title concerned the ethics of biodefense, or the dual-use dilemma. Bibliographies of all selected papers were searched to identify further papers, which were included if they met the same title-relevance criteria.

Twelve articles were identified using the search criteria described above. Of these, two were excluded because they focused on nursing within the realm of biodefense ethics. The remaining 10 relevant articles were thoroughly reviewed and analyzed.

Of the final 10 articles, seven specifically addressed the dual-use dilemma. The remaining three addressed various aspects of the dual-use dilemma without specifying it by name (e.g., instead referring to it as a "double-edged sword") (Sutton, 2005).

Results

Within the peer-reviewed life-science literature, the most commonly suggested strategy for minimizing the potential harm that could be caused by scientific research was self-regulation within the scientific community, followed by increased security within the scientific community, international cooperation, and, finally, increased biodefense education for professionals (Atlas, 2005; Atlas & Dando, 2006; Kelley, 2006; Sutton, 2005; Wright, 2004; Atlas & Reppy, 2005; Revill & Dando, 2006; Somerville, 2005). One article suggested that decreases in security would minimize the risk of dual-use by bioterrorists through increased open scientific scrutiny and self-regulation within the community (Saha & Saha, 2004). Another article argued for the need for more clarity in guidelines to define what type of research poses a need for increased security (Anonymous, 2005). Figure 1 shows a distribution of suggestions for minimizing risks posed by dual-use research from reviewed articles.

Among the articles that suggest self-regulation, a bottom-up approach, ideas for how this regulation needs to occur, vary substantially (Atlas, 2005; Atlas & Dando, 2006; Kelley, 2006; Atlas & Reppy, 2005; Revill & Dando, 2006; Somerville & Atlas, 2005; Saha & Saha, 2004). One article suggested that life scientists take a Hippocratic Oath similar to the one physicians take to become more aware of the issues surrounding dual-use research and their ethical responsibilities (Revill & Dando, 2006). Another suggested even stricter peer-review guidelines stipulating that work should be reviewed not only for quality but also for its dual-use potential (Kelley, 2006). Most articles agreed that the main responsibility for biosecurity needs to be placed directly in the hands of researchers: “Scientists must be encouraged through their own culture of responsibility to work for our security and the public good” (Saha & Saha, 2004).

Many articles also recommended increased security, or a top-down approach (Atlas, 2005; Atlas & Dando, 2006; Kelley, 2006; Atlas & Reppy, 2005). Suggested increases in security ranged from physical security measures such as tighter security for laboratories, stored samples, and research data, to rigorous background checks for staff, graduate students and faculty, and limitations on access to information and knowledge on a strict need-to-know basis (Atlas, 2005; Kelley, 2006). Others suggested that security measures should involve federal oversight through laws designed to prevent publication of certain types of studies or data that could be useful to terrorists, or through enhanced law enforcement activities such as inspections or data confiscation (Atlas, 2005; Atlas & Dando, 2006).

There are currently many international ethics guidelines such as those pertaining to human rights and principles of war. Following increased self-regulation and security, the next most common suggestion for increased biodefense was international cooperation (Atlas & Dando, 2006; Sutton, 2005; Wright, 2004; Saha & Saha, 2004. The focus of this option is a search for collective security, suggesting a “strength in numbers” approach. Proposals for this type of cooperation focus first and foremost on establishing a clear international consensus on bioethical approaches to protection from bioterrorism; one article stated specifically that an international code of conduct should be created to define ethical behavior for all life scientists (Sutton, 2005). Other articles suggested the necessity of international treaties and frameworks limiting the development of dual-use research (Sutton, 2005; Wright 2004). Interweaving the ideas of self-regulation
and applying them to international cooperation, another article suggested that information should be openly accessible to the global scientific community, but the community should be responsible for protecting itself against hostile misuse of the knowledge (Atlas & Dando, 2006).

Education is another important component of protection against dual-use research (Atlas, 2005; Kelley, 2006; Revill & Dando, 2006). One article suggested the development of an ethics module and implementation of the ethical element in all life-science-related curricula (Revill & Dando, 2006). Such ethics modules already exist for some undergraduate bioscience programs, but are limited in scope and rarely detail the possible misuse of research programs by terrorists. Other than education within the formal setting, it would also be useful to offer on-the-job training and guidance to professionals who currently conduct biological research (Atlas, 2005).

In contrast to all other studies, one article recommended decreases in security in order to minimize the risks of dual-use (Saha & Saha, 2004). This article argued that curtailing a terrorist’s access to scientific research also restricts access by the general public and other scientists, a barrier to scientific progress. Furthermore, it argued that hostility caused by increased security could limit researchers’ desires to conduct vital research. It argued instead for the ideas presented above: education, self-regulation, and free flow of information.

**Conclusions**

In a post-9/11 world, the dual-use dilemma poses difficult questions for ethicists and researchers alike. A thorough review of the current life-science literature (MEDLINE only) on dual-use and biodefense ethics yielded self-regulation within the scientific community as the most commonly suggested strategy to minimize the risks posed by dual-use research. Increased security was the second most commonly suggested measure, followed by international cooperation, education, clarity of definitions, and decreased security. Many articles mentioned more than one of the preceding measures, often grouping them together. It is easy to see that one commonly follows from the next, such as increased education, leading to both increased international cooperation and increased security measures. Many of the measures were suggested to be used in tandem to offer increased protections against terrorist use of dual-use research.

This study had several limitations. Ten articles were identified for the study, thus limiting sample size and the ability to detect significant differences, or to make generalizable conclusions. Another limitation is the use of only peer-reviewed literature, which represents a small portion of studies carried out throughout the world. Finally, only one database (MEDLINE) was searched for inclusion into this study and it is possible that the search failed to identify all relevant articles.
Despite these limitations, this study provides important suggestions for methods that can be used to minimize the risks of dual-use research. Further research is necessary to confirm these findings and to provide a detailed plan of action, which incorporates the suggestions described in this study.

References


Biosafety “Behavioral-Based” Training for High Biocontainment Laboratories: Bringing Theory into Practice for Biosafety Training

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Abstract

As the number of individuals working in high biocontainment laboratories (BSL-3 and -4) increases over time, human error remains one of the most important factors in the origin of hazardous incidents in laboratories. With support from the National Institutes of Allergy and Infectious Diseases (NIAID), the Southeast Regional Center of Excellence for Emerging Infections and Biodefense (SERCEB) supported construction of a mock BSL-4 laboratory for training on the Emory Campus, and development of a curriculum for BSL-3 and -4 training. In close collaboration with the Centers for Disease Control and Prevention (CDC) and other scientists and safety professionals, the Rollins School of Public Health has developed one-week, intensive behaviorally-based (“hands-on”) training courses for those working in BSL-3 and BSL-4 laboratories. Since January 2005, over 200 scientists, graduate students and staff have successfully participated in these courses, and the evaluations have been excellent. Long-term evaluation of participants’ knowledge retention...
and practice is still needed. Separately, we are collaborating with scientists and safety professionals at individual institutions to develop tailored onsite training programs for individuals at their own facilities. In addition, we are planning video and distance-based electronic modules for biosafety training.

Background

In the past five years, the United States government has dramatically increased its investment in research with dangerous pathogens, with $1.5 billion appropriated to NIAID and National Institutes of Health (NIH) for bio-defense research in 2006. New laboratories will be used to conduct additional research on dangerous pathogens, from the highly pathogenic avian influenza to anthrax and botulism. Concomitant with the growth in research is a heightened concern that the work be conducted safely. The goal of biosafety is to minimize the risk of infection to individuals workers and reduce the potential for introduction of a pathogen into the community at large. In addition to potential health consequences, laboratory-acquired infections, or fear of them, may create public fear and outrage that could impair the ability to conduct critical scientific research.

Work with dangerous pathogens has been conducted safely in high biocontainment laboratories, such as the BSL-4 laboratories at the CDC for more than two decades. These high-containment settings typically have engineering controls such as air-handling systems and biosafety cabinets, which minimize both the risk of exposure to individuals working in these environments as well as the potential for release of a pathogen into the community.

Human error, however, remains one of the most important factors at the origin of hazardous incidents (WHO, 2006). Those individuals working in high biocontainment laboratories must be trained in safe laboratory practices. Historically, workers in high biocontainment laboratories have completed an introductory occupational health program, and extensive mentoring by senior staff has been required. These individuals must demonstrate successful and safe laboratory behaviors before being granted the freedom of working independently in a high biocontainment laboratory.

Today, biosafety is strongly influenced by the inherent liability of the employer to protect employees and the ability to satisfy public interest that adequate steps have been taken to prepare and train individuals working in these high-containment laboratories. In addition, the United States Department of Health and Human Services (HHS) Select Agent Regulation (42CFR73) mandates additional requirements for biosafety training of individuals before entering the laboratory environment.

As the number of individuals requiring training in safe practices in high biocontainment laboratories increases, standardized introductory biosafety training may be helpful. Such biosafety training may prove useful not only for those entering biocontainment laboratories for the first time, but also for others, including seasoned staff, whose responsibilities include assuring safe laboratory practices among all staff, and exploring safer methods for handling these highly dangerous pathogens. It is important to emphasize that standardized training alone should not replace the intensive one-on-one mentoring needed over extended periods of time (months to years) by a thoroughly seasoned laboratorian.

NIAID at the NIH recently funded 10 Regional Centers for Excellence (RCEs) in biodefense and emerging infections. SERCEB, as part of its scientific portfolio, determined that the demand for biosafety training in high biocontainment laboratories would be increasing. David Stephens, MD, of Emory University, proposed to build a mock BSL-4 laboratory on the Emory campus to support biosafety training in collaboration with scientists and biosafety personnel at the CDC. We believe this was the first mock BSL-4 laboratory in the United States built solely for the purpose of training; it has been used to train individuals in BSL-3 and BSL-4 biosafety practices.

Unlike most previous programs related to high biocontainment biosafety, the program we developed is behavioral-based and focuses on hands-on training in the mock laboratory (Figure 1). The knowledge, attitudes, and perception of laboratory staff about biosafety, including their confidence in their own skills, are an important part of this program as well.

Methods for Course Development and Implementation

Theories are used as the basis for program development. As defined, a theory is a set of integrated ideas, definitions, and suggestions, which allows for a systematic study of an event or situation through the identification of relationships among variables in order to explain and predict the circumstance (Glanz, Lewis, & Rimer, 1997). Using the PRECEDE-PROCEED planning model (Green & Kreuter, 1999), key informant interviews were conducted with experts at the CDC, the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), Emory University, biosafety officers, facility managers, and animal care specialists at the BSL-3 and BSL-4 levels to identify current needs and review existing biosafety training resources. Existing gaps and biosafety issues were listed, the causes for these gaps and safety issues were identified, and a set of 25 behavioral learning objectives were developed. The Science and Safety Course was then developed and implemented as a one-week course of intensive practice, lecture, and examination that focuses on key learning objectives. Evaluation of the 25 key learning objectives occurs through both written and observational examinations. Each day, participants master approximately six learning objectives that are measured and evaluated using a written and observational examination at three stages: pre-training, during training, and
post-training. The written examination is 25 essay questions (each question is worth four points and makes up the pre-assessment) four quizzes, and the final assessment, while the observational examination allows faculty members to observe and evaluate participants based on behavior that takes place throughout the training program. The questions serve as indicators for participant achievement of learning objectives during the four training days.

To successfully master these learning objectives, the Science and Safety Training Program places participants in practical situations. Seasoned scientists and biosafety professionals facilitate discussions during lecture sessions, challenge participants with case studies in a learning team environment, and utilize experts who share personal experiences that focus on the daily learning objectives.

Laboratory Activities
Participants spend 30% of the training program in a laboratory setting. Each participant is asked to master proper donning and doffing procedures according to mock laboratory standard operating procedures (SOPs), including laboratory inspection of engineering controls, spill clean-up, sharps handling, animal escapes, risk assessment, needle-sticks, cuts, animal bites, and life-threatening emergency response situations (Figures 2 and 3). For example, participants are reminded of directional airflow each time a door is opened as alarms sound until doors are closed. Participants must demonstrate checking manehilic gauges and reading signage before entering the laboratory. Faculty is frequently hanging signs on doors asking participants to perform a particular behavior; if the participant does not demonstrate this behavior, they are approached and asked to read the signs. Faculty also tear holes in personal protective equipment (PPE) to ensure that proper inspection of PPE takes place by all participants. Exercises such as these serve as key reminders of appropriate and safe behavior for all participants returning to work in high biocontainment laboratory environments.

In another role playing scenario, faculty makes a hole in a glove and fills the glove with fake blood. The participant is asked to play the role of an individual who receives a cut, passes out and falls to the ground while walking to the sink. These activities are designed to reinforce effective biosafety practices and allow participants to practice these behaviors under close supervision of experienced faculty.

Learning Team Exercises
Participants spend 30% of the training working together to develop constructive approaches to several case studies. In one exercise, participants are asked to construct a laboratory and place equipment in the appropriate areas. In another example, participants develop communication messages while discussing an incident that occurred in a high-containment laboratory. Participants are also asked to conduct risk assessments, package samples, properly receive mailed samples, review published laboratory incidents to determine what went wrong and finally, to develop a solution to prevent future incidents. These learning team exercises allow participants to work together as a team to solve problems. This reinforces the 25 key learning objectives identified by expert staff. In a small and non-threatening environment, participants are
also introduced to the concept of biosecurity and led in discussions of the dual-use research dilemma.

**Examination and Lecture Session**

Participants spend 30% of their training completing written and observational examinations and listening to a lecture summarizing their daily activities. Examinations are always administered before the lecture, because the lecture reviews the learning objectives of that day. Typically, it takes about two days before participants get used to this method and learn that answers will not be provided to them, and they need to work together and seek out the correct answers in participant materials and through the laboratory and learning team sessions. Faculty observe strict adherence to the testing policy and do not discuss answers to the written and oral examination. This places the responsibility on the participant and holds them accountable for their personal learning experience. Additionally, it brings the participants together and by the third day (regardless of their professional background) everyone is working collaboratively to complete the course successfully.

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**Figure 2**
Examples of Science and Safety BSL-3 laboratory activities. Participants are asked to clean a spill (left) and doff PPE following standard operating procedures (right).

**Figure 3**
Participants respond to don BSL-4 PPE (left) and participate in several emergency response exercises, including medical emergencies (right).
Expert Seminars

Participants spend 10% of their training listening and participating in a discussion of biosafety based on expert experiences. Experts discuss how the environment can be modified based on the characteristics of individual pathogens to make it a safer work environment. Other discussions focus on select agent program development, shipment and receipt of laboratory packages, mistakes and lessons learned specific to working in high-containment laboratories, and risk communication and community perception of high-biocontainment laboratories.

Results and Evaluation

Identifying 25 key learning objectives provides a tool for the development of an evaluation process. The success of each participant is determined through observational and written examinations, providing expert faculty the opportunity to witness the growth of each participant on a daily basis. This produces statistical curves for each learning objective (Figure 4). Since the development of the program, over 200 students have been trained using the Science and Safety Training Program, with individuals trained either at their own facility, or onsite at the Emory mock laboratory. Both programs have been successful in terms of test scores of individuals in practical and written exercises. Historically, participants average an approximate score of 25% on the initial written examination, 75% on the second written examination, and 95% on the final written examination. Only one participant was unable to complete the course, demonstrating the curriculum’s ability to challenge individuals with a wide range of educational backgrounds.

This training model allows faculty to monitor participants very closely. In past training programs, scoring of the written examination (in addition to personal observation of practices) has allowed faculty to identify participants who are having difficulties with the material and experiencing high levels of anxiety around the issue of working in the laboratory environment. The written examination serves as an effective discovery tool for identifying participants experiencing, but not physically demonstrating problems they may be having relative to working in a high biocontainment laboratory.

Participants are also asked to evaluate each module and the overall training program. Evaluations are reviewed, summarized and shared with all participating faculty in a “hot-wash” session. If participants report having problems with a particular module, staff and faculty work to develop solutions for the next biosafety course. Overall, participants have rated the course as excellent and would recommend it to others.

Discussion

The behavioral-based biosafety training curriculum has demonstrated successful learning experiences for participants from a wide range of educational backgrounds.

Figure 4

June 2006 BSL-3 Science and Safety statistical curve that measures competency of 25 learning objectives among participants. Each of the 25 learning objectives is worth four points and participants are measured pre-training (lowest curve), during training (middle curve), and post-training (highest curve).
Good laboratory practices are behaviors that must be sustained over extended periods of time. For sustained behavior to occur, individuals must understand the risk of poor laboratory practices, have access to resources that aid in good laboratory practices, practice the skills needed to be successful, and believe in their abilities to carry out good laboratory practices (Bandura, 1994; Hochbaum, 1958; and Rosenstock, 1997). Participants become aware of this concept and begin to identify enabling factors at their institutions, which can be used to promote safer laboratory practices.

During this course, participants report being equally challenged, demonstrating effective learning curves, and comparing this course to a biosafety “boot-camp,” which (as stated by most participants) laboratory scientists and staff should complete. Regardless of effective learning curves and positive participant feedback, the ultimate evaluation is the lack of infections, or other adverse events resulting from occupational exposure. Success of the program will be best judged by the safety record of participants, which, in turn, is dependent on institutional mentoring and practices as well as on the program.

Evaluations of participants in the programs by their supervisors following the course would be useful in assessing the course’s success, and as an additional guide for future course modifications. It would also be of interest to know if the practices that participants learned in the course have resulted in the adoption of safer practices by their colleagues practicing in the same laboratory.

Conceptually, the Science and Safety Training Program has four phases: a) general communication to all participants and supervisors about the organization’s commitment to biosafety and science; b) general biosafety training course for all individuals working in the laboratory setting; c) agent specific training for all individuals working in the laboratory setting; and d) job specific training for all staff working in the laboratory (Figure 5). The Science and Safety Training at Emory University is phase two of four phases needed for a complete and successful biosafety training program.

The Science and Safety Training Program has been packaged and taken to a BSL-3 laboratory, and tailored and implemented to fit the specific needs of that environment. Over 100 individuals were trained, demonstrating similar learning curves and participant evaluations. Additionally, leadership staff at the laboratory facilitated phases one through four, and staff reported feeling more empowered and safer when considering the work they would be asked to do with infectious disease agents.

Even after participants complete all four phases of the Science and Safety Training Program, the program can never replace the value, or importance of professional mentoring that should take place for all staff working in high-containment laboratories. Every scientist and staff member who is new to working in a biocontainment laboratory should be closely observed; they should not be allowed to work alone until a seasoned practitioner is assured that the individual is exhibiting consistently safe practices. This practice is a priority, and must take place to assure individuals working in these environments are adequately prepared and consistently demonstrate the behaviors needed to be safe and effective in high biocontainment laboratories.

In January 2007, Emory University and SERCEB hosted a national conference to bring professionals from the Regional Centers of Excellence (RCEs) and from the Regional and the National Biocontainment Laboratories (RBLs, NBLs) to share their biosafety training programs.

**Figure 5**

Before working in a high-containment laboratory, staff should: participate in a general communication session, practice and demonstrate competency of general standard operation procedures (biosafety practices), understand the details of the agents found in the laboratory, and practice standard operating procedures within their specific job functions.
and to exchange ideas for improving their long- and short-term training programs. All participants expressed a need for enhanced training opportunities in biosafety and the need for continued mentorship after standardized training.

The Emory University Science and Safety Training Program (www.sph.emory.edu/CPHPR/biosafetytraining) is currently developing other training for high biocontainment laboratories, including training programs for emergency response activities, training for communicating laboratory issues to media and community organizations, and the development of a leadership program for biosafety professionals. Future trainings will be developed based on needs identified by participants of Science and Safety Training Programs and feedback provided at professional biosafety and scientific conferences. Initiatives for evaluating the effectiveness of the Science and Safety Training program are presently underway.

Acknowledgements

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References


Reliability of ULPA Filters in Air Handling Systems

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Abstract

Eighteen ultra low penetration air filters were installed in exhaust air systems in a microbiological high containment facility. Their performance was measured annually for integrity and efficiency. After seven years, their reliability was comparable with that of high efficiency particulate air filters in similar systems and are considered a suitable alternative to the latter.

Introduction

High efficiency particulate air (HEPA) filters having a minimum efficiency of 99.97% for particles 0.3 microns in diameter have been widely used to remove infectious aerosols from microbiological containment laboratories and animal rooms (Abraham, Le Blanc Smith, & Nguyen, 1996). The standards to which filters are manufactured and tested have been reviewed (First, 1996).

Ultra low penetration air (ULPA) filters (Liu, Rubow, & Pui, 1985; Avery, 1986) having a minimum collection efficiency of 99.997% for particles in the size range of 0.1 to 2 microns have been developed to provide higher efficiencies for removing particles from air for clean room technologies (Kapoor & Gupta, 2003; Schroth, 1996). ULPA filters have been used where dust-free environments are required for microelectronic, computer and pharmaceutical manufacturing industries. However, they
have not been used for removing infectious particles from exhaust air streams in microbiological facilities.

The efficiencies of both HEPA and ULPA filters measured by aerosols of polydisperse sodium chloride were measured to be 1,000 and 10,000 fold higher respectively than the manufacturer’s minimum specifications (Jamriska, Martin, & Morawska, 1997).

Where microbiological biocontainment in laboratories and animal facilities is important, HEPA filters form a critical component of microbiological barriers. As air handling systems in buildings run continuously, the integrity and efficiency of HEPA filters must be checked at defined intervals to ensure that biocontainment standards are met. In general, annual testing of filters is adopted to ensure the integrity of the filter medium, the efficacy of the filter seal in its housing, and that the pressure drop across the filter is acceptable. Reports describe the reliability and performance characteristics of HEPA filters in nuclear (Carbaugh, 1982), both nuclear and non-nuclear (Robinson et al., 1985) and microbiological laboratory (Abraham, Le Blanc Smith, & McCabe, 1999) installations.

Prior to the availability of data (Jamriska et al., 1997) to verify the efficiency of HEPA filters, ULPA filters were installed in exhaust air ducts in several microbiological high hazard areas of the Australian Animal Health Laboratory (AAHL) to provide an anticipated higher level of aerosol containment. This report compares the seven-year performance of ULPA filters with that of HEPA filters in similar air exhaust systems.

Materials and Methods

610 x 610 x 292 mm HEPA filters were supplied by Gelman Sciences (Australia) and ULPA filters by Flanders Filters (USA). The manufacturing data provided was:

HEPA Filters: Gelman HEPA absolute type model 7590, arrestance efficiency >99.995%, penetration of rated airflow <0.005%, rated airflow 472 L s⁻¹, penetration at rated airflow <0.0003%, resistance at rated airflow 239 Pa, tested in accordance with BS 3928 sodium flame test.

ULPA filters: Flanders-laminar flow grade VLSI ULPA filter model 0-012-6-07-00-SU-33-00-gg-6, serial number V 235958, test flow 100FPM (velocity), efficiency @ test flow 99.99999% @ 0.12 microns, filter size 610 x 610 x 150 mm, dimple pleat construction, no separators.

The laboratory design, air handling systems, filter installations and HEPA filter specifications at the AAHL have been described previously (Abraham et al., 1996 and 1999; Jamriska et al., 1997). Laboratories, animal rooms and support service areas are all enclosed within an outer microbiological barrier. One hundred percent fresh air is drawn from outside the building into a common plenum, and large particulate matter is removed by pre-filters prior to final filtration through HEPA filters to its final destination. For higher hazard zones, including animal rooms, two HEPA filters are used in series for the supply air to ensure against any infectious particle backflow. Air is exhausted from laboratories and animal rooms through clarification pre-filters prior to filtration through two 610 mm square HEPA filters (or in this case, one HEPA and one ULPA filter) in series. All filters are housed in separate cylindrical canisters with removable ends, and sealed in mountings using compressible gaskets that meet required standards for airtightness measured by cold dioctyl phthalate particle penetration. Where two filters are installed in series, both filters are integrity tested sequentially.

Eighteen ULPA filters were installed in four selected laboratories and 14 selected animal rooms. In such rooms, two HEPA filters in series for exhaust air systems is the normal installation configuration. All ULPA filters were installed in the secondary exhaust position following a standard HEPA filter. After initial installation and commissioning, each filter was tested annually to confirm the absence of leaks around the gasket seals for the filter housings and to ensure that the pressure drop across the filter face was within operating limits. The scan testing of ULPA filters to demonstrate filter integrity conformed to the Australian Standard 1807.6 (2000) and was identical to that done routinely for HEPA filters in other parts of the facility.

Results

Over a seven-year period from 1995 to 2002, five of the 18 ULPA filters were replaced by standard HEPA filters for non-conformance with the performance criteria. The reasons for these replacements are shown in Table 1.

<table>
<thead>
<tr>
<th>Replacement Reason</th>
<th>Laboratories (4)</th>
<th>Animal rooms (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Media leak</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Gasket seal failure</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Media blockage</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Still in service</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 1

Numbers of ULPA filters replaced in room exhaust systems within seven years.
Discussion

This report analyzes the performance of 18 ULPA filters in continuous use in air exhaust systems in containment laboratories and animal rooms. Five (28%) were replaced in the first seven years of operation, which compares with 18.4% of HEPA filter replacements in the same period of service in a previous study (Abraham et al., 1999). Like the previous study, there were three main reasons for filter replacement; defects in the filter medium, failure of the gasket seal holding the filter in place, and blockage of the filter medium. Due to the small numbers in this study, the percentages of filter failures in each category were not statistically significant.

All of the ULPA filters were installed in the secondary position behind a primary HEPA filter. Blockages were measured by the pressure drop (generally, rising from 200 to 500 Pa) across the filter by Magnehelic gauges and confirmed by subsequent air flow measurements through the filter directly. Filters in the secondary position are expected to be impacted by fewer larger particles and should be less susceptible to media blockage; the data supports this view. The origin of the blockages is unknown, but is probably particulate matter. Although only one ULPA filter was considered blocked in this study, ULPA filters do not appear to block more readily than HEPA filters in similar positions.

Although testing in workshop conditions has demonstrated the high filtration efficiency of ULPA (and HEPA) filters (Jamriska et al., 1997), sensitive methods to prove their continued performance in the field are not routinely available. During this study, the same cold dioctyl phthalate (DOP) tests used to screen HEPA filters were done annually to identify significant faults in ULPA filters. It was this test that allowed for the detection of filter media leaks and gasket seal leaks and the replacement of non-performing filters (Table 1). However, the cold DOP test does not demonstrate the continued high efficiencies of either HEPA or ULPA filters whilst in service. This study shows ULPA filters can be used in air exhaust systems in a large containment laboratory and function reliably for at least seven years.

Acknowledgements

The proposal to install ULPA filters was pioneered by David Martin. Rob Dandy, Neil Slater, and Ross Cook did the majority of the monitoring of air filters and their careful attention to detail is gratefully acknowledged. Steven Edwards and Mat Bojnic offered constructive comments on the manuscript.

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The CODE RED Solution—Biothreat Response Training for First Responders

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Abstract

The terrorist events of 2001 brought to light the need for a close working relationship between the first responder communities and the public health laboratories in New York State (NYS). Since 2002, the Wadsworth Center’s Biodefense Laboratory (BDL) has been providing outreach training to first responders in New York, to enable them to respond safely, correctly, and confidently to biothreat events. A pocket trifold was developed, titled “CODE RED,” which describes sampling protocols, risk analysis criteria, and important contact information for use during an emergency response to a potential bioterrorism situation. In addition, the BDL has provided training to more than 1,000 first responders in the basic knowledge of biothreat agents, routes of dissemination, sampling and decontamination methods, contamination control protocols, biothreat risk assessment, and legal chain of custody procedures. The training methods have been established for use by first responders wearing personal protective equipment (PPE). All states can benefit from highly trained first responders who are capable of efficient, safe, and effective biothreat response, resulting in increased safety of the first responders and laboratorians, as well as decreased turnaround times for laboratory results. The CODE RED trifold provides a working model for training first responders at the state and county levels for emergency biothreat response.

Background

Since 2002 the New York State Department of Health’s Wadsworth Center Biodefense Laboratory (BDL) has been involved in outreach training of NYS first responders, to provide them with the knowledge and tools needed to respond safely, correctly, and confidently to biothreat events. The first biothreat sample was received at the Wadsworth Center in 1999. Although preliminary communication lines had been established between law enforcement and the laboratory, it quickly became apparent that the two groups’ perspectives on sample collection and packaging differed significantly. The laboratory gave instructions that a triple containment system should be used during the collection and packaging of the suspect sample. Once the sample had been received by the laboratory, however, it became evident that the need to use three layers of easily removable, sealable Ziploc bags had not been stated clearly and the interpretation of the instructions by the responding sample collection team had been quite different. The sample that arrived was triply contained with layers of duct tape. Although this containment system did indeed meet the laboratory’s stated requirement for three layers, and it did prevent any material from leaking out during transport, it also required the laboratorians to work strenuously for over four hours to open the package safely within the Biosafety Level 3 (BSL-3) laboratory. This first sample foreshadowed the events of 2001, when 906 samples were received by the Wadsworth Center following the intentional release of anthrax in the mail system; 24 of these samples tested positive for the weaponized bacterium. The laboratory staff expanded from three laboratorians to more than 20, through the redirection of experienced staff from other laboratories to assist with sample triage, receipt, processing, documentation, and testing.

Several other BSL-3 laboratories within the Wadsworth Center had their normal work suspended, so that teams of two laboratorians could process samples around-the-clock in order to meet the urgent demands of sample testing and reporting. It soon became apparent however, that these samples were only the beginning and this influx would not subside until 2002. The New York State Police Forensic Investigation Center became the triage site for all samples intended for processing at the laboratory, and the state police soon found themselves inundated with mostly noncredible samples. The ability of the state police to quickly determine threat level and to decide which samples required priority testing proved to be an invaluable asset, allowing the laboratory to focus only on priority samples and avoid dedicating resources and time to risk/threat assessments. However, the laboratory continued to receive credible samples that were improperly packaged for rapid high-priority testing.

These packaging problems proved to be time-consuming and cumbersome and at times posed a danger to personnel working in the BSL-3 laboratory. Improperly packaged samples can take two to three times longer to process and have the added danger of cross-contamination (i.e., contamination of the laboratory itself and of samples subsequently tested there), a factor that must be taken very seriously within a public health testing facility. The consequences of a contaminated laboratory are enormous; all testing within the larger facility may need to be suspended to ensure the safety of the personnel, as well as the integrity of the scientific testing.
Wadsworth Center’s laboratories worked meticulously and cautiously with each sample, regardless of packaging or credibility, to ensure that neither the laboratory nor the staff were compromised or contaminated during this event. But this impressive track record does not negate the stress on the laboratory staff or the additional time needed to process low-risk or improperly packaged samples.

In early 2002, as the influx of samples began to subside, it became clear that the laboratory had a new task beyond its ongoing response to and testing of biothreat samples—namely, the training of first responders in biothreat response. A mechanism was needed to inform all first responders of: 1) the potential risks associated with response to a biothreat situation; 2) the appropriate personal protective equipment (PPE) required; and 3) the importance of information-gathering for use in risk assessments. A concise and easy-to-use protocol needed to be devised and deployed, so that first responders in the state would know how to collect and package a biothreat sample in a manner that would not only protect the first responder from accidental infection or contamination but also would provide the testing laboratory with an appropriate sample that was safe and easy to process.

Integral to this information outreach protocol would be contact information available to the first responder community on a 24-hour, seven-day per week basis (CDC, 2006). In early 2003, the New York State Department of Health released the CODE RED trifold brochure to first responders and laboratories in the state; since then, approximately 5,000 CODE RED trifolds have been distributed. This initial trifold has since evolved into an extensive training course, tailored to each audience’s specific level of expertise, and has been provided to more than 1,000 first responders and law enforcement personnel throughout New York State.

The CODE RED Solution

The CODE RED Trifold

The CODE RED trifold (Figure 1) is a wallet-sized card that is divided into four basic sections—Section 1: Materials, PPE, and Contact Information (Figure 2); Section 2: CODE RED mnemonic (Figure 3); Section 3: Risk Assessment Criteria (Figure 4); and Section 4: Annotated Collection Procedure (Figure 5).

The CODE RED Training Program

To effectively communicate the information highlighted on the CODE RED trifold, a training module has been developed to give first responders basic knowledge of biothreat agents, routes of dissemination, sampling and decontamination methods, contamination control protocols, biothreat risk assessment, and legal chain of custody procedures. Additionally, these training methods have been established for use by first responders wearing PPE ranging from Level C to Level A.

The training module is offered in a range of formats depending on the specific requirements of the first responder team. The basic CODE RED training is a three-hour class that focuses on information on biothreat agents, followed by an overview of the CODE RED collection procedure and biothreat risk assessment training. An initial demonstration allows participants to see several simulated collections taking place; the demonstrators emphasize techniques that will protect the first responder and minimize the potential for cross-contamination. The
participants are then given a post-class test, in which they assess the risk in multiple mock biothreat events and participate in hands-on sample collection, providing them with the opportunity to become familiar with the specific roles described in the CODE RED collection procedure.

This basic training module is provided to first responders at the local level who are routinely involved in response to isolated, lower-credibility biothreat incidents. Approximately 800 local law enforcement, fire, Hazmat and emergency medical technicians have participated in this basic training module. By using a train-the-trainer format, local representatives are encouraged to return to their respective agencies and train additional first responders in their communities on the use of the CODE RED trifold in a biothreat event.

The CODE RED training module has also been expanded into a two-day training session with more in-depth background information and an intensive hands-on training session. Participants are involved in multiple collection scenarios designed to cover a wide array of possible situations. The second day of the in-depth course is a multi-scenario drill that incorporates the use of specific levels of PPE (from Level C to Level A), multiple sample collection types, personnel and sample decontamination procedures, situation briefing/debriefing and radio communications. This hands-on drill emphasizes the importance of using a two-person collection team, and allows participants to explore how to best incorporate this technique into their existing incident command framework.

The advanced CODE RED training module has been provided to state and Federal first responders because of their involvement in large-scale biothreat event response. Since 2005, this advanced training course has been provided to approximately 80 NYC Office of Fire Prevention and Control (OFPC) officers in order to ensure that OFPC personnel throughout the state have been adequately trained, and are familiar with using the CODE RED protocols while wearing Level A PPE.

Additionally, advanced training has also been provided to 22 members of the National Guard 2nd Civil Support Team and 80 members of the NYC Police Contaminated Crime Scene Emergency Response Team (CCSERT). In conjunction with the NYC OFPC, the NYC Centers for Environmental Health and the NYC Department of Environmental Conservation, the Wadsworth Center has begun to expand the CODE RED training module to include Chemical, Radiation and Unknown Hazard Response training in an effort to provide NYC with a comprehensive response plan to terrorist events (Markenson et al., 2005; U.S. Department of Homeland Security, 2006). Currently, however, the CODE RED trifold is not intended for use in the event of a chemical or mixed-agent release and all samples deemed a credible biothreat should be pre-screened in the field for explosive, chemical or radiological threats prior to being transported to the laboratory for testing.

The overall success of the CODE RED training program stems in part from the integration of key training
aspects, including the use competent instructors, well-developed course materials, extensive hands-on training, and easy accessibility to the program (Clizbe, 2004). Wadsworth Center personnel travel throughout New York State providing tailored CODE RED training to interested first responder communities free of charge. This system relieves local agencies of any financial burden associated with personnel travel or instructor costs, and ensures a high level of participation in the training session. Organizations interested in obtaining CODE RED training contact the Wadsworth Center BDL through their local Bioterrorism Coordinators, local law enforcement agencies or local health departments.

The CODE RED Collection Kit

To provide a consolidated approach to biowar emergency response within NYS, a CODE RED Collection Kit was designed and has been made available, free of charge, to all first responder communities. The CODE RED Collection Kits include all materials needed to properly package and decontaminate two to three biothreat samples, and a hard-sided transport container that will ensure the safe transport of the samples to the laboratory.

A key component of the success of the collection kit has been the involvement of both the laboratory and the first responders in its design and implementation. The laboratory evaluated sample testing methods and prepared the first kit prototype to meet all the required laboratory safety standards. The kit was then evaluated by first responders in varying levels of PPE, since it was critical both that the first responders are able to follow the protocol and that the kit components are easy to handle in all types of situations. The resulting kit is easy to store, and includes sterile, certified collection materials, a CODE RED trifold, an annotated CODE RED Sample Collection Procedure, and a Biothreat Risk Assessment Questionnaire. Most importantly, the state-wide deployment of the CODE RED Collection Kits ensures that all first responders are utilizing the same techniques, protocols, and materials, giving the laboratory added confidence in the integrity of the biothreat sample, and facilitating sample testing.

Overall Impact

The CODE RED solution has had a significant impact on the relationship between first responder/law enforcement communities and the state public health laboratory.

First Responders

First responders have gained confidence in dealing with biowar situations by having a clearly defined protocol to follow. The hands-on training provided in addition to the CODE RED trifold gives law enforcement officers a basic understanding of the agents that are most likely to be used as bioweapons and bolsters their confidence for the implementation of the sampling protocols.
during future events. The easy integration of the CODE RED sampling protocol into existing law enforcement protocols is an important factor in the general acceptance of these techniques within this non-laboratorian based community. The ability to make sound risk assessments during response to an event has decreased the level of anxiety in the first responder community as well as the amount of effort dedicated to the collection and submission of non-credible samples. Additionally, first responders have become aware of the willingness of the BDL to aid them in risk assessment analysis, collection/sampling approaches, and appropriate levels of emergency response.

The provision on the CODE RED card of 24/7 contact information has increased the communication between the laboratory and the first responders, further solidifying this invaluable working partnership (Werner, 2005). After-hours calls are received by a state-wide duty officer who in turn contacts the director of the BDL for communication with the agency involved in the bioterror event.

State Public Health Laboratory

In 2002, the number of samples submitted for bioterror testing decreased, reflecting a decrease in the nation’s threat level. However, following the introduction of the CODE RED solution in 2003, the BDL staff immediately noticed two important changes in sample workload. First, the number of non-credible samples submitted decreased, due to more effective risk assessments taking place, which in turn further decreased the overall number of samples being submitted for testing. Second, as the CODE RED sampling protocol began to be implemented in the field, samples that came into the laboratory were properly packaged, and critical information needed for priority testing assessment was included. This led to a two- to three-fold decrease in sample processing times, greatly improved turnaround times (from sample processing, testing and final results reporting) and allowed the laboratory to restrict highly focused testing to only the higher-priority samples. Although improperly packaged samples still do, on occasion, arrive at the BDL, the CODE RED Training Solution has provided the laboratory with a feedback and training mechanism to ensure that the submitting agency becomes aware of, and its personnel properly trained in, the sample collection and submission requirements.

Limitations

The most significant limitation of the CODE RED solution is the large number of first responders who require training within New York State. Over 70,000 police officers alone could benefit from this training; however, with a training staff of three, the BDL is not capable of personally training each of these first responders in the CODE RED solution. Additionally, high staff turnover, retirements, and loss of lives in 2001 pose a significant problem in maintaining the number of trained NYS first responders at a maximum. The use of the CODE RED trifold, along with a train-the-trainer format, helps to ensure that all first responders have access to critical information even if they do not directly participate in a CODE RED training module.

Conclusions

The CODE RED solution has helped to bridge the gap that previously existed between the first responder communities and the public health laboratory within New York State. The increased collaboration and information exchange between laboratorians and law enforcement has begun a shift in our community’s response to not only biological, but also chemical and radiological, threat response. The integration of the two groups’ priorities and limitations ensures that first responders are adequately trained and equipped to respond to a wider array of hazards, and that the laboratory is capable of testing the collected samples. The CODE RED solution has provided New York State with a mechanism to unify the various groups involved in public health emergencies, thereby strengthening the state-wide emergency response system.

Acknowledgements

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References


Capsule

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What’s new? What’s hot? What’s timely? If you don’t have time to search the Internet for the latest developments that might impact your work environment, you just might find some of this information in the “Capsule” column. Please e-mail any comments or suggestions to ekrisiunas@aol.com or to Co-Editor Barbara Johnson at barbara_johnson@verizon.net or Co-Editor Karen B. Byers at karen_byers@dfci.harvard.edu.

Master Plan and Laboratory Safety Helps the CDC Keep Pace with Expanding Public Health Challenges

This writer first went to the Centers for Disease Control and Prevention (CDC) in Atlanta for an epidemiology course in 1988. My how things have changed! From its inception in 1946 to the present, the CDC has saved lives and improved the health and welfare of people around the world in countless ways. The 21st century brings fresh challenges to those who provide the nation’s and the world’s first line of defense against threats to public health. Consider that in the last 25 years, the CDC has participated in the discovery of more than 30 new infectious diseases and agents ranging from Ebola hemorrhagic fever to Legionnaire’s disease. Visit the following link for more information.

MMWR July 20, 2007/56(28)—Notice to Readers: Revised International Health Regulations Effective for the United States

On July 18, 2007, the revised International Health Regulations (IHRs) entered into effect for the United States. IHRs are an international legal framework designed to help contain, or prevent serious risks to public health, while discouraging unnecessary or excessive restrictions on travel or trade. The revised IHRs: 1) describe the obligations of World Health Organization (WHO) member states to assess and manage serious health threats that have the potential to spread beyond their borders; and 2) provide guidance for meeting those obligations.

www.cdc.gov/mmwr/preview/mmwrhtml/mm5628a5.htm

NIOSH Pocket Guide to Chemical Hazards

Over the years, many of us have used the NIOSH Pocket Guide to Chemical Hazards (NPG). The orange covered, spiral bound text was always easy to spot in my personal text library. The (NPG) is intended to be a source of general industrial hygiene information on several hundred chemicals/classes for workers, employers, and occupational health professionals. The NPG does not contain an analysis of all pertinent data; rather, it presents key information and data in abbreviated or tabular form, for chemicals or substance groupings (e.g., cyanides, fluorides or manganese compounds) that are found in the work environment. The information found in the NPG should help users recognize and control occupational chemical hazards. An electronic version is available at the following web site:
www.cdc.gov/niosh/npg/

Hospital eTool Laboratory Module

Useful training material is available at the OSHA web site. There are “eTool” modules for various industries, including healthcare. The eTool* for healthcare focuses on some of the hazards and controls found in the hospital setting, and describes standard requirements as well as recommended safe work practices for employee safety and health.

*eTools are stand-alone, interactive, web-based training tools on occupational safety and health topics. They are highly illustrated and utilize graphical menus as well as expert system modules. These modules enable users to answer questions and receive reliable advice on how OSHA regulations apply to their work site. As indicated in the disclaimer, eTools do not create new OSHA requirements. The laboratory module can be located at the following link:
www.osha.gov/SLTC/etools/hospital/lab/lab.html

The Biosafety Clearing-House

The Biosafety Clearing-House (BCH) is an information exchange mechanism established by the Cartagena Protocol on Biosafety (http://bch.biodiv.org/about/protocol.shtml) to assist parties in implementing its provisions and to facilitate sharing of information on, and experience with, living modified organisms (LMOs). For more information visit the following link. The site is part of the United Nations Environment Program (UNEP).
For additional information, visit the following link:
http://bch.biodiv.org/default.aspx
Do you have a biosafety question and you’re not sure who to ask? Send your questions to the “Ask the Experts” column and I’ll get them answered for you. Drawing from my own experience or that of other experts in the field, we’ll try to compile a thorough and comprehensive answer to your question. Please e-mail your questions to jkeene@biohaztec.com or Co-Editor Barbara Johnson at barbara.johnson@verizon.net or Co-Editor Karen B. Byers at karen_byers@dfci.harvard.edu.

Shortcuts Not an Option When it Comes to Risk Assessment and Biosafety Manuals

Why is the performance of a risk assessment so important?

It is apparent that we have concentrated our risk assessments based on the pathogenicity of organisms for man, and in some cases animals, but is this the real basis of risk assessment? It is true that the original reasoning for the biosafety levels, as defined in the Centers for Disease Control and Prevention/National Institutes of Health (CDC/NIH) Biosafety in Microbiological and Biomedical Laboratories (BMBL) was to minimize the potential for the risk of occupationally acquired infections in laboratory workers. Unfortunately, biosafety professionals and Principal Investigators have tended to look at the risk assessment process in light of the BMBL only, and have not examined the overall picture of potential risk to laboratory workers and the environment (the community, including plant and animal exposure). This shortsighted view of risk assessment could result in serious liability for an institution, especially since the recommended guidelines in the BMBL are minimal guidelines for the protection of workers against possible exposure.

The primary objective of physical containment should be to confine organisms in order to reduce the potential for exposure of laboratory workers, persons outside the laboratory, and the environment to organisms which have been determined to be hazardous to one or more of these entities. Any risk assessment should be based on a realistic evaluation of the potential for the agent in question to cause any problems should it be released in any way or form from the laboratory.

Different conditions require different procedures and containment requirements. For example, an experiment to study the pathogenicity of a fungus that causes infection in wheat might have an entirely different risk assessment if performed in the middle of Manhattan, New York, as opposed to the same research being performed in Manhattan, Kansas. It is critical to perform a realistic assessment of the potential damage caused should the organism escape from the laboratory. This seems at times, to be a difficult concept to understand for a researcher who does not view the agent as pathogenic, but rather, as a tool to study a specific metabolic pathway, or to produce a protein, particularly when that researcher has “always used this organism and never had a problem.”

Sometimes the experiment must be modified for reasons other than the potential for release of infectious agents. I recall a particular instance when a researcher came to me with a new recombinant Bacillus species that carried the gene for making the external coat protein of a particularly dangerous viral pathogen. He wanted to put this organism into a fermenter and produce large quantities of the viral antigen. The risk assessment began with the question: “Does the recombinant Bacillus form spores?” His answer was “No, well at least not many.” The next question posed was, “Then it does form spores to some extent?” To which he answered, “Well, yes.” The answer to the following question was problematic: “What antibiotic was used to select for this particular organism?” “Oh, that’s easy; it is resistant to antimegasus (fictional antibiotic to protect the innocent).” This particular answer also completed the risk assessment and the final determination was that you can’t put this organism into the fermenter in this fermentation plant.

Now, there was actually no danger of infection from this organism, either as the Bacillus itself, or from the protein that it produced, but there was a concern on the part of the fermentation plant operator. It so happened that “antimegasus” was the main product for this particular facility, and the antibiotic was the major antibiotic used when people were allergic to a similar antibiotic produced in other facilities. From a corporate standpoint, it was not feasible to take the risk to put a spore-forming bacillus, resistant to “antimegasus” and carrying the gene for production of a pathogenic virus coat protein, in this particular fermentation plant. The risk of release of the spore-former with its viral coat protein, along with its concomitant contamination of the company’s “cash cow,” was not acceptable. Therefore, the experiment was not allowed to continue and the researcher went back to the drawing board to develop a similar organism that was not resistant to the antibiotic in question.

Physical containment begins with the realistic review of the potential danger, and is achieved through the use of specifically designed laboratory practices, containment equipment, and special laboratory design. There are no shortcuts and each risk assessment is unique to the facil-
ity in which the work is to be performed. No matter how much you may want to do it, you cannot use someone else’s risk assessment.

**Does anyone out there have a biosafety manual I can use/copy/plagiarize?**

Simply copy the BMBL word-for-word and your work is done. Wrong! The BMBL publication is by definition “guidelines” and minimal guidelines at that. Each facility and each laboratory within the facility is a unique entity, and the biosafety manual that serves the facility, or laboratory must be equally unique. This concept fits with the concept of risk assessment discussed above. It is important for the biosafety manual to reflect the needs of the risk assessment. The BMBL is the skeleton upon which you and the PI place the meat of the specific safety requirements for the laboratory. Those requirements are based on the potential for release of an organism, or its product to the environment, and the hazard to workers associated with performing the specific protocols in the specific laboratory.

Do you want to build a good biosafety manual? If so, start with the BMBL; then take each section and determine how you are going to specifically meet those requirements within your laboratory while performing your particular protocol. For example, the BMBL states that access to the laboratory must be controlled while experiments are being performed. Your manual should indicate that access to the laboratory is controlled by placing appropriate signage at the door to the laboratory prior to initiating work with the agents, and must be enforced by laboratory personnel working in the laboratory. Note that the BMBL states what should be done; the safety manual states how you will do it in your laboratory.

The days of starting an experiment that was just dreamed up without significant planning on the part of the PI and the lab staff are long over. If we are going to have to develop a protocol for conducting an experiment, then we should take the time to complete the risk assessment and to develop appropriate safety protocols to match. Safe operation is not only good for lab workers; it improves the science and the experiment.

Remember, the biosafety manual is not a static document that is developed, put on the shelf, and never looked at again. It is a dynamic document that must change as the experiments progress and protocols change. It is work, but it is work well worth doing.

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**Biosafety Tips**

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Biosafety Tips brings you practical approaches to biosafety or “news you can use.” If you are looking for a useful and sensible solution to a biocontainment problem, or perhaps a reference to help convince a skeptical researcher of the need for caution, this is the place to look. In this column, I share biosafety insights for managing a variety of workplace situations. I welcome feedback and suggestions for future topics. Please e-mail any comments or suggestions to karen_byers@dfci.harvard.edu or to Co-Editor Barbara Johnson at barbara_johnson@verizon.net.

**Brucella Outbreak in Clinical Microbiology Laboratories**

An overview of laboratory-associated infections reported in the past 75 years is published in the Chapter entitled “Epidemiology of Laboratory-Associated Infections” (Harding & Byers, 2006). The source literature on these infections provides detailed case reports that are useful for training purposes. Biosafety Tips in Volume 12, Number 1, summarized reports of laboratory-acquired infections with *Neisseria meningitidis* in clinical microbiologists. In every case, a single microbiologist was infected through droplet, or aerosol transmission from routine identification procedures conducted on the open bench.

This column describes a report in the *Journal of Clinical Microbiology* of an airborne Brucella outbreak in 31% of the clinical microbiology staff of a community hospital (Staszkiewicz et al., 1991) and two publications (Sue et al., 1989; Ruben et al., 1991) that describe secondary cases of Brucella infection.

**Background**

Brucella is a zoonotic pathogen and, outside of the laboratory, presents an occupational risk for farmers, veterinarians, and abattoir workers. Approximately 200 cases of human brucellosis are reported annually in the U.S. In Michigan, where this outbreak occurred, eight cases were reported between 1983 through 1987 (Staszkiewicz et al., 1991).
Index Case
One clinical microbiologist had an illness in July described as “self-limited and hepatitis-like.” Ten weeks later the same microbiologist was hospitalized and diagnosed with brucellosis based on blood cultures positive for presumptive Brucella species and an anti-Brucella antibody titer of 1:640.

Outbreak Description
When the diagnosis was reported to the hospital, all staff in the microbiology laboratory, as well as adjacent clinical laboratories, were given serological tests and a questionnaire for clinical symptoms and non-laboratory risk factors for Brucella infection. The serologic tests indicated that eight of the 26 microbiologists had antibodies to Brucella. The survey revealed that one microbiologist had been ill in May, in addition to two in June, and one in July. Three staff members later became ill in August, and one fell ill in September. All had received an initial diagnosis of nonspecific viral illness. Clinical features included myalgia and back pain; in addition, 75% had abnormal liver functions and weight loss. Five of the seven staff who reported an illness on the survey had a positive blood culture (63%), even though only one of the staff members (the index case) was acutely ill when the blood cultures were drawn. None of the 49 staff in adjacent laboratories were infected; all eight infected staff members were clinical microbiologists.

Source Investigation
Staff members had no risk factors other than working in the laboratory, and no one recalled working with Brucella in the previous two years. The story of this actual investigation is as thorough as any in the scripts of the CSI television series. The only possible source was a single isolate from an outbreak of eight cases in a clinical laboratory. It was reported that the strain manipulated in the laboratory, and no one recalled working with Brucella in the previous two years. All infected staff were treated with antibiotics; one had a relapse and was retreated with a different combination of antibiotics. All staff members recovered completely.

How Did the Exposure Occur?
No spills or incidents were reported, but all 8 employees worked in the lab on March 30 and 31, as opposed to five of 18 seronegative employees. The article includes a floor plan with Xs marking the predominant laboratory workspace of the Brucella cases, as well as the location where the Brucella manipulations occurred—on the open bench. The laboratory did have a biosafety cabinet in the Parasitology/Mycobacteriology laboratory; however, it was not used for the Brucella manipulations. This resulted in the airborne transmission of Brucella.

Outbreak Identification
This case study illustrates the difficulty in identifying laboratory-acquired infections that do not have a distinctive diagnostic feature. The infected staff had a wide range of non-specific symptoms (from serious illness requiring hospitalization to a subclinical infection) and incubation times after exposure ranging from six weeks to over five months. Fortunately, the source investigation included a review of freezer contents, since no log records were kept for stock manipulations. This community hospital did not have much experience handling Biosafety Level 3 (BSL-3) pathogens. To prevent re-occurrence, the microbiology laboratory adopted the policy that all work on presumptive, or confirmed Biosafety Level 3 organisms such as Brucella would be conducted in the biosafety cabinet at all times. In addition, plates of these BSL-3 organisms are sealed when not in use.

Secondary Laboratory-Acquired Infection
The Staszkiewicz article has a chilling addendum: “In March 1989, a laboratory worker at the Centers for Disease Control became infected while working with our isolates. A break in technique was not identified. Inspection of the laboratory revealed that the biologic safety cabinet was in working order.” Biosafety professionals attending the 32nd ABSA conference in 1989 heard a presentation entitled “Investigation of a Laboratory-acquired Brucella melitensis Infection: Confirmed Case Due to Biovar 3, A Strain Responsible for a Previous Outbreak at Another Institution” (Suen et al., 1989). The talk described the first laboratory-acquired infection in the 26-year career of a microbiologist; it was also the first infection in 27 years at this CDC reference laboratory. It was reported that the strain manipulated was an isolate from an outbreak of eight cases in a clinical laboratory outbreak of Brucella. Although the geographic location of the outbreak is not named it seems likely that this is the same Brucella outbreak. In describing this secondary case, the authors stated: “No specific accident or incident could be identified as leading to the infection, but several of the biosafety recommendations for this agent (referring to BMBL) were not being practiced” (Suen et al., 1989).

Secondary Transmission to Spouse
Another secondary case is described in a third publication (Ruben et al., 1991). One of the clinical microbiologists in the laboratory outbreak was hospitalized on July 18 and released on July 24 with oral antibiotics. Two days later, he was re-admitted and discharged after additional IV medication. The blood cultures drawn during both hospitalizations were negative; urine and sputum cultures were normal. After the laboratory outbreak was confirmed, and his serum titer for Brucella antibody was determined to be 1:640, the lab worker was reexamined...
and treated with an additional three months of antibiotic therapy. All symptoms resolved; he returned to work in September 1988, and his antibody titer dropped to 80, indicating a resolved previous infection. However, in February 1989, his wife was admitted to the hospital with fevers, chills, headache, and myalgias. Brucella was isolated from her blood culture and the CDC reference laboratory confirmed that her blood culture isolate was identical to the outbreak strain. Person-to-person transmission does not commonly occur in Brucella; however, it was suspected in this case. The wife had not visited the microbiology laboratory in years and had no other risk factors for Brucella infection. Sexual relations with the infected husband had occurred infrequently during his acute illness June through September, but resumed in October 1988, before his antibiotic treatment for brucellosis was completed. No culture evidence for sexual transmission was obtained from either spouse, but the author advises that it would be prudent to abstain from unprotected intercourse during treatment for Brucella.

References


Molecular Biosafety

Margy S. Lambert
University of Wisconsin—Madison, Madison, Wisconsin

The molecular biology and biotechnology fields are growing by leaps and bounds. Molecular Biosafety aims to shed light on how these cutting-edge techniques impact safety. Please e-mail your insights and questions to Margy Lambert at mlambert@fpm.wisc.edu or Co-Editor Barbara Johnson at barbara_johnson@verizon.net or Co-Editor Karen B. Byers at karen_byers@dfci.harvard.edu.

Safety Advance: Transposon Gene Delivery Systems

What do the terms “piggyBac,” “Sleeping Beauty,” and “Frog Prince,” have to do with biological safety? These transposons as well as others, such as Tol2, Mos1, and Himar1, are being used in the development of nonviral DNA/gene delivery systems. The relevance to safety is that nonviral delivery methods have the primary advantage over viral vectors of being noninfectious.

Transposons, or transposable elements, are DNA elements that can move or “transpose” from one location in a DNA molecule to another location, either on the same or a different DNA molecule. The phrase “jumping genes,” coined from Nobel Prize winning scientist Barbara McClintock’s research with maize, may be a more recognizable expression. Transposases are the enzymes that catalyze the DNA movement. The development of gene delivery systems, commonly referred to as vectors, is often driven by the goal of creating safer and more effective human gene therapy options.

Viruses have the capacity to enter host cells and direct host machinery to produce the components necessary for infectious viral particles (Knipe et al., 2007). Some viruses, such as retrovirus, lentivirus, and adenovirus, can integrate into the host genome with the potential result of chronic or latent infections. Integration can also result in insertional mutagenesis if the viral DNA integrates near a gene such as an oncogene. Use of replication-deficient viral vectors greatly minimizes the chance that infectious progeny viruses will be generated. The possibility of infectivity is not eliminated; however, because replication-competent viruses can arise through a recombination mechanism. Viral vectors’ major advantage over nonviral methods is the ability to achieve stable expression. In particular, retroviral and lentiviral vectors can integrate into the host genome to achieve long-term expression of the gene of interest. Another potential advantage of viral vectors is the ability to target specific tissues. Tissue tropism is exhibited because viral entry is limited by the type of receptors displayed on
the cell membrane surface, which varies by tissue type.

Disadvantages of viral vectors include the potential for pathogenicity/infectivity, induction of immune inflammatory responses, insertional mutagenesis, and frequently the need to use a higher level of precautions. The risks of replication-deficient viruses gaining the genes necessary to become replication-competent or of retroviruses/lentiviruses integrating near a crucial gene such as an oncogene and activating its expression are slight. However, these risks often necessitate the use of biosafety level 2 (BSL-2) precautions and containment.

The most common nonviral delivery route is via plasmids. Plasmids are extrachromosomal DNA rings that replicate independently of genomic DNA and provide a widely-used versatile tool for manipulating and moving genes from cell to cell. Plasmid vectors have the advantages of simplicity, safety (noninfectious components), and lack of immune activation. BSL-1 precautions and containment are appropriate for use of the vast majority of plasmid vectors. Advances have been made in nonviral delivery methods, but until recently, the major drawback of these systems has been the inability to achieve persistent expression due to loss and degradation of plasmid DNA in living tissues.

A recent advance has been the use of plasmids that include transposons and transposases. Transposon systems overcome the main drawback of simple plasmid delivery systems since the transposases integrate the genes of interest into the host chromosomes resulting in stable expression (Baliunas et al., 2006; Miskey et al., 2003; Wu et al., 2006). Transposase activity can then be turned off to stop movement of DNA. Transposon vectors offer a major step forward in safety because of the elimination of the infectious component of viral vectors. However, insertional mutagenesis remains a potential drawback of transposon delivery systems.

Transposases such as Sleeping Beauty have the advantage of near-random integration sites as compared to retroviral/lentiviral vectors that tend to integrate into actively-transcribed regions of the genome. The ease of manipulation of transposon vectors allows for modifications such as coupling of transposases to DNA-binding domains to achieve targeted integration (Kaminski et al., 2002). The use of such chimeric transposases could further improve the safety of transposon vectors by targeting integration to “safe” regions of the genome not associated with oncogenesis.

Sleeping Beauty (a synthetic transposon derived from fish) was constructed and demonstrated to be capable of transposing DNA from a plasmid to a human chromosome 10 years ago (Ivics et al., 1997). Since then, a number of transposon systems have been developed and used successfully to obtain stable gene expression in mammalian cells. Transposon vectors have been used effectively in primary and established mammalian cells from various lineages (Huang et al., 2006) as well as in animal models of gene therapy (Liu et al., 2006). Recently, a new strategy has been devised that uses the piggyBac transposon (derived from a moth) for production of transgenic animals (Shinohara et al., 2007).

There are still many unknowns in the development of transposon vectors, including remaining questions on technical as well as safety issues. The use of such vectors, however, offers a great opportunity to maximize the advantages and minimize the drawbacks of existing delivery systems. Transposon delivery systems combine the ability to achieve stable gene expression with the use of safer noninfectious components. In addition, the incorporation of targeted integration mechanisms into transposon systems could significantly decrease the insertional mutagenesis risk. The potential safety benefits alone merit consideration of this method.


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Contact: Phone: 1-866-425-1385 or 847-949-1517; Fax: 847-566-4580; E-mail: absa@absa.org; www.absa.org

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Vicon Publishing, Inc.–Lab Manager Boot Camp One-Day Conference
Massachusetts Medical Society in Waltham, Massachusetts
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Principles & Practices of Biosafety
Sheraton Austin, Austin, Texas
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American Biological Safety Association (ABSA) 51st Annual Conference
John Ascuaga’s Nugget, Reno, Nevada
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October 18-21, 2009
American Biological Safety Association (ABSA) 52nd Annual Conference
Hyatt Regency Miami, Miami, Florida
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October 3-6, 2010
American Biological Safety Association (ABSA) 53rd Annual Conference
Hyatt Regency Denver at Colorado Convention Center, Denver, Colorado
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October 30-November 2, 2011
American Biological Safety Association (ABSA) 54th Annual Conference
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