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Biosafety Risk Assessment Methodology

Susan Caskey*, Jennifer Gaudioso*, Reynolds Salerno*, Stefan Wagener[+], Mika Shigematsu[++], George Risi[+++], Joseph Kozlovac[#], Vibeke Halkjær-Knudsen[##], Esmeralda Prat**

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Abstract

Laboratories that work with biological agents need to manage their safety risks to persons working the laboratories and the human and animal community in the surrounding areas. Accepted biosafety best practices and international guidance span a wide variety of biosafety risk mitigation measures, which can be categorized as engineering controls, procedural and administrative controls, and the use of personal protective equipment. The determination of which mitigation measures should be used to address the specific laboratory risks should be dependent upon a risk assessment. Ideally, a risk assessment should be conducted in a manner which is standardized and systematic allowing it to be repeatable and comparable. A risk assessment should clearly define the risk being assessed and avoid over complication.

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Acronyms

ABSA – American Biological Safety Association
BSL – Biosafety Level
CEN – European Committee for Standardization
CDC – Centers for Disease Control and Prevention
DOE – Department of Energy
IRGC – International Risk Governance Council
MCDA – Multi-Criteria Decision Analysis
WHO – World Health Organization

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Executive Summary

Laboratories that work with biological agents need to manage their safety risks to persons working the laboratories and the human and animal community in the surrounding areas. Accepted biosafety best practices and international biosafety guidance spans a wide variety of biosafety risk mitigation measures. These measures can be categorized as engineering controls, procedural and administrative controls, and the use of personal protective equipment. The determination of which mitigation measures should be used to address the specific laboratory risks should be dependent upon a risk assessment. Ideally, a risk assessment should be conducted in a manner which is standardized and systematic which allows it to be repeatable and comparable. A risk assessment should clearly define the risk being assessed and avoid over complication.

Many laboratories lack the knowledge and skills to conduct a structured and systematic risk assessment, as a result most biosafety risk assessments are based purely on subject matter expert opinion These assessments lack repeatability, are difficult to compare, and difficult to communicate. Often laboratories default to the minimum regulatory requirements, or relyon rules to define biosafety practices rather than utilize the recommended risked based approach to biosafety risk mitigation.

Ideally, a risk assessment scheme which defines specific frequency of exposure and infection as well as specific consequences of disease would be created. . Currently, there is limited frequency data to define the probability of an infection or an exposure, which makes implementing a pure quantitative risk assessment for biosafety problematic. Likewise, there is limited data to quantify the consequence of disease in a host. This begs the question, how can a structured systematic biosafety risk assessment be conducted?

There are a couple of key points to regard about biosafety; biosafety and infectious disease expert opinions are valuable and provide a great deal of information on the accepted potential of exposure, infection and can be used to define the consequences of disease. The risks associated with biosafety consist of multiple factors which include the properties of the biological agent, laboratory factors, and environmental factors. Not all of these factors will impact the risk in the same manner. Based on these key elements, this project has developed a biosafety risk assessment methodology and accompanying model which uses a multi-criteria decision analysis process to structure and provide a systems approach to assessing biosafety risks.

This methodology and model were developed by partnering with biosafety and infectious disease experts from around the world. This partnership was used to create the methodology, and specifically define and detail the models described in this report. The resulting models have undergone review by international laboratories working with a variety of biological agents and based upon the positive feedback from these laboratories; both the process and the detailed models are presented in this report.

Introduction

Sandia National Laboratories' International Biological Threat Reduction department has been working with biosafety, infectious disease, and risk experts to develop a systematic and

standardized methodology for biological safety risk assessments. This standardized methodology will enhance biosafety risk assessments by allowing them to be both repeatable and quantifiable. This methodology is not intended as an all-hazards assessment, but is focused on the risks associated with biological materials being handled in a laboratory setting.

In the 1940's and 1950's a number of studies[1] demonstrated the abundance of laboratory-acquired infections within bioscience laboratories. These infections were caused by poor safety practices and procedures as well as a lack of safety systems in the laboratories. Beginning in the 1970's and 1980's, laboratory biosafety became an emerging professional discipline. Laboratory biosafety is a combination of systems and practices intended to reduce the risk of accidental exposure to or release of agents that cause infectious disease. Implementation of biosafety is generally based on a risk assessment, which historically has been a subjective and qualitative process that relies heavily on expert opinion and unique personal experiences. There is general consensus on the high-level risk assessment process, which can be broken down into three steps that start with the identification of the biological agent or hazard. Once the hazard has been identified and its unique properties have been researched and established, the second step is normally the assessment of the probability of such a hazard to cause an undesired event (exposure, disease etc.), the actual consequence. It is obvious that the probability will vary significantly based on the handling of the agent (e.g. procedures performed) as well as the control measure in place. The third step is the management of the risk through established control measures and reassessment if necessary.

Although risk assessments are currently performed in the biosafety community, there is no unified approach and appropriate quantitative tools do not exist. The lack of a clearly structured process makes biological risk assessment highly variable and inconsistent.

With the dramatic rise in biotechnology worldwide, the current methods for conducting a risk assessment using predetermined biological safety risk group classifications may no longer be sufficient. Different national and international institutions have developed their own scheme for defining agent risk groups and the risk assessor can modify the agent's risk based upon how that agent will be used in the laboratory. This risk-group process is based upon expert opinion dating back at least 20 years, and does not adequately reflect new bioscience research or biosafety technologies and methodologies. Moreover, the results of such risk assessments are solely qualitative and highly variable. Many experts believe this is a significant problem, especially with the recent rapid expansion in the number of high containment research facilities and the increasing amount of work with dangerous biological agents. Specifically, many leading international biosafety experts have recently called for the development of a structured, more quantitative biosafety risk assessment methodology.[2] Even the World Health Organization[3] specifically states regarding risk groups "… simple reference to the risk grouping for a particular agent is insufficient in the conduct of a risk assessment."

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[1] Robert M. Pike, "Laboratory-Associated Infections: Incidence, Fatalities, Causes, and Prevention", Ann. Rev. Microbiol., 1979

[2] Stefan Wagener, Allan Bennett, Maureen Ellis, Marianne Heisz, Kerry Holmes, Joe Kanabrocki, Joe Kozlovac, Patty Olinger, Nicoletta Previsani, Reynolds Salerno, and Terence Taylor, "Biological Risk Assessment in the Laboratory 2nd Biorisk Management Workshop Report", Applied Biosafety Volume 13, Number 3, 2008

[3] World Health Organization, *Laboratory Biosafety Manual Third Edition*, 2004

Furthermore, the biosafety community does not currently practice structured risk management, probably at least in part because the risk assessment process is so poorly defined. Instead biosafety professionals strive to eliminate any chance of an exposure. Without accepted tools to manage risk, they waste scarce resources trying to mitigate all vulnerabilities, which is impossible in a laboratory setting. Additionally, without the use of a structured risk assessment process, the perception of risk either by the biosafety professionals or by the general public often drives the mitigation processes rather than the technical or actual risk. Risk perception should not be discounted in making mitigation determinations, but it should not be the primary driver for risk management decisions; and in making management decisions, a clear distinction between the technical risk and the perceived risks should be understood and documented. A structured and well documented risk assessment which also defines the perceived risks can be used to support biorisk management strategies.

This paper will discuss a risk assessment methodology for assessing the technical risk of laboratory processes and a software tool that implements this methodology. These bothcan help in the standardization of the biosafety risk assessment processes. This methodology is the translation of expert knowledge into a methodology and model that can be utilized by experts and those striving to become experts in the quantification of laboratory biosafety risks.

Risk Analysis Principles

Multi-Criteria Decision Analysis

This methodology is not intended to be a formal quantitative assessment of absolute risk but, rather provide a structured method for the comparison of the relative risks posed by laboratory practices and by biological agents. There are numerous approaches to structured risk assessment and decision analysis; multi-criteria decision analysis (MCDA) is one of these methods. MCDA has been identified as a scientifically sound method for decision analysis and has been extensively validated for use in risk analysis.

"Research on quantitative decision making has proceeded from the study of decision theory founded on single criterion decision making towards decision support for more realistic decision making situations with multiple, often conflicting, criteria, and more than one decision-maker. In particular, MCDA stands out as a promising category within decision support methods."[4]

Linkov[5] and others have advocated the use of a multi-criteria decision analysis as part of a traditional risk assessment in situations where there is a limited set of empirical data and a high level of uncertainty. MCDA is a robust discipline and is useful in illustrating and justifying decisions. MCDA has been accepted by the risk community as a process for conducting structured risk assessments, focusing on areas with limited detailed knowledge, and where information may vary with time. In addition to the structure, MCDA also offers a transparent

[4] Mona Riabacke, Mats Danielson, Love Ekenberg, and Aron Larsson "A Prescriptive Approach for Eliciting Imprecise Weight Statements in an MCDA Process" Algorithmic Decision Theory: First International Conference, 2009

[5] Igor Linkov, "Comments on the OMB Risk Assessment Bulletin", 2006

method for conducting the risk assessment as it can help in quantifying and communicating the risks and support decision-makers choices on risk management. MCDA provides a mechanism to combine multiple information sources including those based upon expert judgment to assess risks. [6]

The basic structure of MCDA models is to define the relevant criteria which define the problem(s) to be addressed, attach numerical measurements and relative importance to the criteria, and to combine the numerical values to arrive at a relative ranking.[7] In MCDA there are several mathematical models which define how the numerical measurements and relative importance rankings are determined. Likewise, combining of measurements varies from model to model. The method used in this analysis is based upon a weighted sum algorithm which is one of the most common approaches. This method combines all the criteria and weights into a single score (*A*) by summing all the weighted numerical values (*aij,wj*).

$$A = \sum_{j=1}^{n} aij, wj$$

When using MCDA for risk analysis, the resulting score of the weighted sum is a component in the creation of the relative risk ranking. In this methodology, the weighted sum is used to define the likelihood and the consequences independently. These two values are combined to create the relative risk characterization.

Risk Governance

Risk governance[8] aims at providing a framework for an organization to enable risk assessment and risk management activities to take place in a sustainable way. While improving decision making, planning and prioritization, it contributes to a more efficient allocation and use of the resources within an organization. From this standpoint, risk management is seen as a process that creates value by ensuring that the resources consumed by risk management and control are used efficiently to guarantee the sustainability of the activities and the achievement of the strategic objectives. Risk governance should appear thus as a central part of any organization's strategic management.

Risk governance is based on thorough risk assessment, sound decision making, strict and consistent implementation of appropriate risk mitigation measures, monitoring and reviewing.

Biorisk management is also based on risk assessment[9]. Biological risk assessment is a legal obligation in many countries that have biosafety regulations[10], as part of the notification or

[6] Igor Linkov, F. Kyle Satterstrom, Jerrery Steevens, Elizabeth Ferguson, and Richard C. Pleus, "Multi-Criteria decision analysis and environmental risk assessment for nanomaterials" Journal of Nanoparticles Research, 2007
[7] Evangelos Triantaphyllou, *Multi-Critera Decision Making Methods: A comparative Study*, Kluwer Academic Publishers, 2000
[8] White paper on Risk Governance, The International Risk Governance Council, 2006 http://www.irgc.org/The-IRGC-risk-governance-framework,82.html.
[9]Terms used in relation to risk assessment are based on those of draft ISO Guide 73, "Risk management - Vocabulary", 2009 (http://www.npc-se.co.th/pdf/iso31000/ISO_DGuide_73_(B).pdf).

authorisation process and/or as a basis to determine the required containment levels and other protective or preventive measures. It is also a major element of the WHO laboratory biosafety manual and a basis of the laboratory biorisk management standard CWA 15793[11].

As stated in the IRGC Risk Governance Framework[12], risk assessment is preceded by a pre-assessment step aiming at providing a structured definition of the problem and identifying how it may best be handled. It supposes capturing a variety of issues at a strategic level, without omitting any of the risk-related factors that could have a significant impact on the activities. Pre-assessment includes a "risk framing" that ensures a common understanding of the risk issues by all stakeholders. The next step, risk appraisal, includes a technical risk assessment as well as a concern assessment that aims at identifying the perception of the stakeholders as well as possible sociological, economical and political consequences and implications. Results of the risk appraisal are then judged regarding risk tolerability and acceptability, which corresponds to risk evaluation according to the ISO terminology[13]. Decisions are made on this basis, and implementation of the risk management approach is then carried out accordingly. Communication is a major component of the whole process.

As part of the larger goal of strengthening laboratory biorisk management, the IRGC Risk-Governance framework offers an important structure for understanding that societies have different organizational capabilities for assessing and mitigating biorisks as well as different societal notions of what biorisk embodies. As such, the IRGC framework is useful for discussing the challenges to implementing a international norm of biorisk governance from both organizational and a political perspectives.

Discussion on Risk Acceptance

This methodology provides a structured method of categorizing the risk; however, this methodology does not evaluate the absolute level of risk. Unless the risk is eliminated, there will always be some level of risk; determining if the risk is acceptable, controllable, or unacceptable is part of the risk management decision. There are several factors which can influence risk acceptance. These factors include such considerations as the level of available resources to mitigate or control the risks, the regulatory requirements overseeing the risk, the value of work to the community, or to the researcher, and the public's general perception regarding the risk.

The public perception of risk is often a driving factor in setting the priorities and the agendas of regulatory bodies. The IRGC recommends considering the public concerns as a separate analysis from the technical risk assessment. Technical experts aim to assess risks based on well characterized factors, and to be objective and rational. The public perception of risk is often based upon hypothetical notions and emotions.[14] The emphasis of this methodology is on the technical assessment and characterization of the risks.

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[10] National regulations implementing Directives 90/219/EEC (now replaced by 2009/41/EC) and 2000/54/EC in the European Union; "Regulation on the Biosafety Management of Pathogenic Microbiology Laboratories", 2004, in China; "Biological Agents and Toxins Act," Singapore 2005.
[11] "Laboratory biorisk management standard", CWA 15793:2008 (ftp://ftp.cenorm.be/PUBLIC/CWAs/wokrshop31/CWA15793.pdf).
[12] http://www.irgc.org/IMG/pdf/IRGC_WP_No_1_Risk_Governance__reprinted_version_.pdf
[13] http://www.npc-se.co.th/pdf/iso31000/ISO_DGuide_73_(B).pdf.
[14] Paul Slovic, *Public Perception of Risk*, Journal of Environmental Health Volume 59, Issue 9, 1997.

However, the risks associated with public perception should not be ignored. There are some key factors which can be used for evaluation of public perception. Decision Research studies conducted in 1978 compared perceptions of risks of 30 activities and technologies, and the studies conducted in 1984 on the same data refined the factors based upon the interrelationships. Two parent factors, dread and the unknown, were defined in the 1984 study. The sub-factors for dread include: what is the public's trust that the situation can be controlled, what is the national or global impact, what is the risk to future generations, what is the ability to mitigate the consequences, and did the impacted individual(s) voluntarily engage in the activity. The sub-factors which define the unknown include: is the event observable, is there a delayed effect from the event, has this event occurred previously, and what is the level of understanding of the event prior to the occurrence.

Biosafety Risk Assessment Methodology

As defined by Kaplan and Garrick[15], risk analysis consists of answering three specific questions: what can happen?, what is the chance that it will happen?, and, if it happens, what are the consequences?. The Sandia team worked with internationally recognized biosafety and infectious disease experts to first define what biosafety risks can happen, focusing on biological laboratories and the agents being handled in these laboratories. The list of what can happen provided the set of scenarios or biosafety risks which would need to be addressed in the methodology. This was done in association with the Public Health Agency of Canada. Working collaboratively with these experts, thirteen separate biosafety scenarios where identified.

The scenarios or biosafety risks defined in this methodology are as follows:

1. Risk to individuals in the laboratory
    a. Of an infection caused via droplets or droplet nuclei that have entered the upper or lower respiratory tract.
    b. Of an infection caused through compromised skin or direct injection into the blood stream
    c. Of an infection caused through exposure to the mucosal membranes
    d. Of infection caused via contact with the gastrointestinal tract
2. Risk to an individual outside the laboratory (the human community)
    a. Of an infection caused via droplets or droplet nuclei that have entered the upper or lower respiratory tract
    b. Of an infection caused through compromised skin or direct injection into the blood stream
    c. Of an infection caused through exposure to the mucosal membranes
    d. Of infection caused via contact with the gastrointestinal tract
3. Risk to animals outside the laboratory (the animal community)
    a. Of an infection caused via droplets or droplet nuclei that have entered the upper or lower respiratory tract.
    b. Of an infection caused through compromised skin or direct injection into the blood stream
    c. Of an infection caused through exposure to the mucosal membranes
    d. Of infection caused via contact with the gastrointestinal tract

[15]Stanley Kaplan and B. John Garrick, "On The Quantitative Definition of Risk" Risk Analysis, 1981

4. Risks to humans and animals resulting from a secondary exposure

Biosafety risks, in this methodology, are defined as a function of the likelihood of infection by the agent and the likelihood of exposure through an infectious route based on the procedures and work practices and the consequences of disease assuming infection.

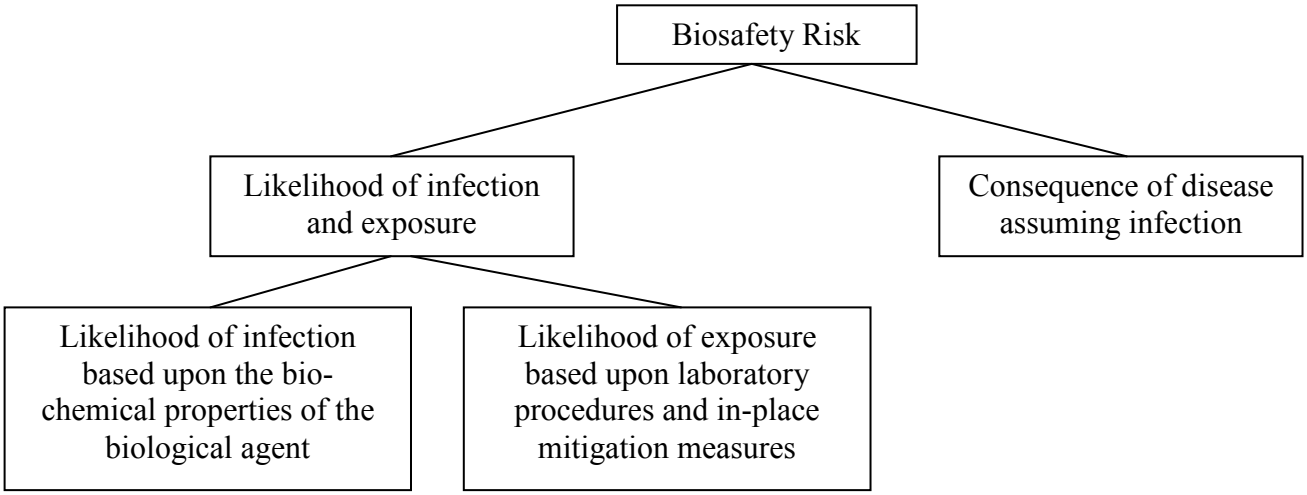

Figure 1: Biosafety Risk Assessment Methodology

The likelihood of infection and the consequences of disease are assessed separately for each of the "at risk" populations; humans and/or animals. Also, the likelihood of infection is defined uniquely for each biological agent to match the agent's potential routes for infection.

The likelihood of exposure is assessed based upon the laboratory procedures and the in-place biosafety measures. Additionally, the likelihood of exposure is reviewed differently for those individuals inside the laboratory and those outside the laboratory.

This methodology combines all the elements for each specific scenario to quantify the separate relative risks for each scenario. These risk calculations can be compared to each other and used to help determine risk acceptance, support risk communication, and to help focus risk reduction efforts.

Biosafety Risk Assessment Models

The models for assessing each of the thirteen risks are unique, but each follow the same basic methodology and have many elements in common. The overall risk assessment methodology looks at specific biochemical properties of the biological agent to define the likelihood of infection and the consequences of disease. The specific properties are similar to those originally used to define biosafety risk groups for biological agents, but due to the transparent nature of this methodology, this process forces the biosafety risk assessors to understand the details of the biological agent they are assessing. Additionally, this model can be easily applied to emerging or modified agents. The properties used to assess the agents were defined by a group of biosafety and infectious disease – (both human and animal) experts.

The elements which capture the agent specific details include: categorizing the specific routes of infection and the infectious dose for each route. The routes of infection are defined by the possible methods (known or preferred routes, possible routes, unknown routes, and known not possible routes) the agent can enter the host system and cause an infection. The infectious dose (ID_{50}) is captured in a manner to highlight a very low or an unknown infectious dose. The exact dose is not required. The dose defined in the model which highlights a very low dose was decided to be an ID_{50} less than 1000. This value was defined by subject matter experts and was based on reviewing the known ID_{50}'s for several biological agents. These factors define the likelihood of infection for each route for each agent. The consequence of disease of a given agent is defined by the mortality rate of those infected, the impact or morbidity on a human host, morbidity rate in animals, agent properties to include the agent's ability to suppress a host's immune system and mutate in the natural environment; and availability of effective treatment and prophylaxis.

This methodology categorizes specific elements of the processes in the laboratory and the in-place biosafety measures to determine the individual's in the laboratory and the community's potential for an exposure. These elements have been defined separately for laboratory workers and members of the biosafety community. The in-place biosafety measures are defined based on standard best laboratory practices. The specific elements are captured in the models as sets of questions. The questions asked, in this assessment, require the assessor to understand the laboratory processes and understand key principles of biosafety. This model was specifically designed to require this level of understanding and knowledge by the user; this allows the model to function as a performance based model designed to support the biosafety community rather than function as a replacement for expert judgment.

The laboratory procedures define the potential of an exposure. The types of exposures which are specifically captured include, the procedures potential to produce an aerosol, to include sharp hazards, to cause contact with the agent, and/or to allow ingestion of the agent. The in-place biosafety measures are reviewed to determine the amount of mitigation each measure provides for the specific exposure hazard. The in-place biosafety measures are organized by engineering controls, administrative controls – to include specific laboratory practices, standard laboratory practices and biorisk management; and personal protective equipment.

Each of the thirteen scenarios defines the likelihood of exposure and infection uniquely; consequences of disease are defined uniquely for humans in the laboratory (considered healthy adults), humans outside the laboratory (consequences are scaled by 5% to account for the healthy worker phenomenon), and animals outside the laboratory. The healthy worker phenomenon was defined based upon discussions with public health experts and reviewing texts[16], for this model an average difference of 5% is used between the health status of people actively working in the community and those living in the community.

The risk of a secondary exposure is defined by the likelihood of an exposure and infection and the agents potential for secondary transmission and associated disease consequences.

[16] Ann Aschengrau and George R. Seage III, "Essentials of Epidemiology in Public Health" Jones and Bartlett 2003

Technical Assessment Scheme

This assessment methodology has defined thirteen specific scenarios (what can happen?) focusing on biological agents being manipulated in a laboratory. To answer the two remaining questions of the risk analysis triplet, what is the chance that it will happen?, and, if it happens, what are the consequences?; separate models were developed for each scenario to define the likelihood and the consequences. The development of each model included several steps: 1. defining the accepted criteria to assess the likelihood and consequences, 2. defining a "scoring system" to evaluate each situation against the criteria using absolute or ratio scales, 3. calculating relative weights for the criteria, since not all criteria will contribute equally to the risk, and 4. developing an equation that would combine the criteria scores and the relative weights to produce a measure of the risk. The Sandia team worked with internationally recognized biosafety and infectious disease experts to establish a set of structured criteria to define each of the models.

Criteria Definitions

The criteria which define the risks for biological agents are defined by those criteria which influence the likelihood of infection and those criteria which define the consequence of disease. The criteria which influence the likelihood of infection are defined to, first, categorize which exposure routes the agent may pose a potential for infection and, second, the likelihood of infection by that route.

Likelihood Models

The models which define the likelihood for each of the thirteen scenarios are unique; specific criterions are used in multiple models. Likelihood of exposure models for humans and animals outside the laboratory are identical, while the likelihood of infection is different for the different hosts. There are eight unique likelihood of exposure models defined in this methodology. For all routes of exposure, the type of biological material (isolated strains, diagnostic samples, and environmental samples) are captured and used to influence the potential for exposure. Also, standard good laboratory biosafety procedures and biorisk management are captured in all the models as risk reduction measures. The specific criteria which define the unique likelihood of exposure models are defined as follows:

1. Unique Elements which influence *the likelihood laboratory of an exposure to individuals in the to droplets or droplet nuclei*
    - Inhalation Exposure potential through laboratory processes
        - Accidental Aerosol
        - Aerosol Experiment
        - Spill
    - Exposure potential through cleaning and maintenance of equipment
    - Exposure potential of animal use in the laboratory
        - Properties of Animals
            - Number
            - Size
        - Multiple Species of animals
        - Shedding potential of animals

    - Animal waste handling

Inhalation Exposure Mitigation measures focused on reducing the potential to individuals in the laboratory

- Primary Containment
- Primary Containment of Animals
    - Animal housing
    - Containment for animal manipulations
    - Containment of animals during transport
- PPE
    - Respirators
- Procedures
    - Special handling techniques
    - Special animal handling techniques

2. Unique Elements which influence the *likelihood of an exposure to individuals (human or animal) outside the laboratory to droplets or droplet nuclei*
    - Aerosol generation through laboratory processes

Inhalation Exposure Mitigation measures focused on reducing the potential to individuals outside the laboratory

- Secondary Containment

3. Unique Elements which influence *the likelihood of an exposure to individuals in the laboratory through compromised skin or direct injection into the blood stream*
    - Percutaneous Exposure potential through laboratory processes
        - Sharps in use in processes
        - Breakable items used in processes
        - Exposure potential through cleaning and maintenance of equipment
    - Exposure potential of animal use in the laboratory
        - Properties of animals
            - Number
            - Size
        - Multiple Species
        - Animals potential and ability to bite or scratch
        - Sharps in use while also handling animals

Percutaneous Exposure Mitigation measures focused on reducing the potential to individuals in the laboratory

- PPE
    - Gloves
- Special handling procedures for sharps
- Primary Containment of Animals
    - Animal housing
    - Containment for animal manipulations
    - Containment of animals during transport
- Special animal handling techniques

4. Unique Elements which influence the *likelihood of an exposure to individuals (human or animal) outside the laboratory caused through compromised skin or direct injection into the blood stream*

- Sharps in use

Percutaneous Exposure Mitigation measures focused on reducing the potential to individuals outside the laboratory

- Specific waste handling techniques for potentially infectious sharps leaving the laboratory

5. Unique Elements which influence *the likelihood of an exposure to individuals in the laboratory to the mucosal membranes*

- Contact Exposure potential through laboratory processes
    - Spill
    - Waste handling processes
    - Laboratory surface types
    - Exposure potential through cleaning and maintenance of equipment
- Exposure potential of animal use in the laboratory
    - Properties of animals
        - Number
        - Size
    - Multiple Species
    - Animals potential to shed biological agent
    - Specific animal waste handling processes

Contact Exposure Mitigation measures focused on reducing the potential to individuals in the laboratory

- PPE
    - Gloves
    - Clothing
    - Protective eyewear
    - Type of shoes worn in laboratory and use of shoe covers
- Specific laboratory procedures
    - Absorbent material use and procedures
    - Handling of items in the laboratory
    - Spill cleanup procedures
    - Protection of broken or damaged skin

6. Unique Elements which influence the *likelihood of an exposure to individuals (human or animal) outside the laboratory to the mucosal membranes*

- Specific waste handling techniques

7. Unique Elements which influence *the likelihood of exposure to individuals in the laboratory through the gastrointestinal tract*

- Exposure potential through laboratory processes
    - Spill
    - Exposure potential through cleaning and maintenance of equipment

Exposure Mitigation measures focused on reducing the potential to individuals in the laboratory

- PPE
    - Gloves
    - Face Shields
- Special Laboratory procedures
    - Handling of items in the laboratory
    - Hands washing procedures

8. Unique Elements which influence the *likelihood of exposure to individuals (human or animal) outside the laboratory through the gastrointestinal tract*
    - Specific waste handling techniques
    - Specific liquid waste handling techniques

The models, which define the likelihood of infection to humans (in and outside the laboratory) and to animals (outside the laboratory), are used to identify the routes of concern for a given agent; and to quantify the potential of infection. Those models are defined as follows:

- *Likelihood of an infection in humans caused via droplets or droplet nuclei that have entered the upper or lower respiratory tract*
    - Is this agent known to cause infection via inhalation (to cause infection via droplets or droplet nuclei that have entered the upper or lower respiratory tract) in a laboratory setting?
    - Is this agent known to cause infection via inhalation (to cause infection via droplets or droplet nuclei that have entered the upper or lower respiratory tract) in the natural environment?
    - Is the infectious dose (ID_{50}) of this agent for this route less than 1000 or unknown?

- *Likelihood of an infection in animals caused via droplets or droplet nuclei that have entered the upper or lower respiratory tract*
    - Is this agent known to cause infection via inhalation (to cause infection via droplets or droplet nuclei that have entered the upper or lower respiratory tract) in the natural environment?
    - Is the infectious dose (ID_{50}) of this agent for this route less than 1000 or unknown?

- *Likelihood of an infection to humans caused through compromised skin or direct injection into the blood stream*
    - Is this agent known to cause infection via percutaneous exposure (to cause infection through compromised skin or direct injection into the blood stream) in a laboratory setting?
    - Is this agent known to cause infection via percutaneous exposure (to cause infection through compromised skin or direct injection into the blood stream) in the natural environment?

- Is the infectious dose (ID_{50}) of this agent for this route less than 1000 or unknown?

- *Likelihood of an infection to animals caused through compromised skin or direct injection into the blood stream*
  - Is this agent known to cause infection via percutaneous exposure (to cause infection through compromised skin or direct injection into the blood stream) in the natural environment?
  - Is the infectious dose (ID_{50}) of this agent for this route less than 1000 or unknown?

- *Likelihood of an infection to humans caused through exposure to the mucosal membranes*
  - Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes) in a laboratory setting?
  - Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes) in the natural environment?
  - Is the infectious dose (ID_{50}) of this agent for this route less than 1000 or unknown?

- *Likelihood of an infection to animal caused through exposure to the mucosal membranes*
  - Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes) in the natural environment?
  - Is the infectious dose (ID_{50}) of this agent for this route less than 1000 or unknown

- *Likelihood of infection to humans caused via contact with the gastrointestinal tract*
  - Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract) in a laboratory setting?
  - Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract) in the natural environment?
  - Is the infectious dose (ID_{50}) of this agent for this route less than 1000 or unknown?

- *Likelihood of infection to animals caused via contact with the gastrointestinal tract*
  - Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract) in the natural environment?
  - Is the infectious dose (ID_{50}) of this agent for this route less than 1000 or unknown?

Consequence Models

The models for consequence of disease assuming infection for humans are focused on the actual disease characteristics in humans. The model for consequence for animals is focused on the agricultural impact to the country or region of the laboratory being assessed. The two consequence models are defined as follows:

- *Consequences of disease in humans assuming infection*
    - Does this agent or one of its by-products cause a carcinogenic or mutagenic reaction in a human host?
    - Does this agent have toxin or enzyme production which has a negative impact in a healthy human host?
    - Does this agent suppress a human host's immune system? (E.g. cause dramatic suppression which renders the host susceptible other infections)
    - Does this agent have the ability to mutate once in a host or in the natural environment to become infectious through new route or new hosts, or to cause increased consequences?
    - What is the duration of illness (the average length of time of clinical signs of infection) in a normally healthy human host?
    - What is the severity of illness (the average severity of illness, ranging from no signs of illness to hospitalize in critical condition) in a normal health human host?
    - What is the duration of infection (the length of time the host is infected with the organism) in a normal healthy human host?
    - Does this disease cause any long-term conditions (sequelae) in a normal healthy human host?
    - What is the frequency of death in humans caused by this disease in a defined population during a specified interval of time (Mortality Rate)?
    - What level of national or international reporting is required for outbreaks of this disease?
    - Do effective diagnostic tests exist for humans?
    - Do post exposure treatments (including immuno-globulin, vaccines and anti-microbials) exist for humans?
    - Do preventative measures (vaccines) exist for humans?

- *Consequences of disease in animals assuming infection*
    - If the agent infects animals, what is the expected morbidity rate to a naïve but otherwise healthy animal population?
    - What level of national or international reporting is required for outbreaks of this disease?
    - What species of animals can this agent infect?
    - Do effective diagnostic tests exist for animals?
    - Do post exposure treatments (including immuno-globulin, vaccines and anti-microbials) exist for animals?
    - Do preventative measures (vaccines) exist for animals?

Likelihood and Consequence model

The model which defines risks of secondary exposures is derived from the likelihood of infection and likelihood of exposure and the consequence of disease models, but also includes specific criteria to define the potential of a secondary infection. These specific criteria are defined as follows:

- Is this agent known to cause infection via vector-borne transmission (to cause infection by direct mucosal membrane contact or percutaneous exposure from a vector (e.g. arthropod))?
- Is this agent known to cause infection via vertical transmission (to cause infection from mother to fetus in the womb or via ingestion of infected breast milk)?
- Is this agent known to cause infection via sexual transmission (to cause infection through sexual contact including intercourse)?
- What is this agent's stability outside of a host?
- How easily does this agent transmit between human hosts?
- How easily does this agent transmit from animal to human hosts?
- How easily does this agent transmit from human to animal hosts?
- How easily does this agent transmit between animal hosts?

Scoring system

Sandia developed a "scoring system" for each criterion. The scoring system is based on an absolute (or ratio) scale[17] with zero defined as the absence of the element defined by the criterion and four defined as the highest level possible value for the element (for some elements the highest possible value is the worst case and for others the highest possible value is the best case). For example, taking the ingestion scenario for an agent which cannot cause infection via ingestion the score will be zero, for an agent which ingestion is the preferred route of infection the score will be four. The values between zero and four were defined to be linear and text was used to provide guidance on how a scenario should be scored. As this tool was designed for use in capturing expert judgment, it was assumed that users may identify the need to use values "in-between" those provided in the model. As the scores are based upon absolute or ratio scales, users can use "in-between" values as long as the ratios are maintained. One example where this feature may be used is under likelihood of exposure for ingestion; the criterion asks about hand washing practices and defines zero as no hand washing and a score of four for hands being washed frequently during the procedure. The user of this model can provide a score of, for example, three if hands are washed but not between every step of the procedure. This scoring system was peer reviewed by biosafety and infectious disease experts. The full set of pre-defined scoring tables is defined in Appendix A.

Model weighting

Following the development of the criteria and the scoring system, Sandia worked with biosafety and infectious disease experts, in partnership with the American Biosafety Association, Colorado State University, and the Public Health Agency of Canada, to weigh each criterion for each model. To determine the relative weights, Sandia worked with the experts to conduct a pair-wise comparison using semantic scales for all the defined criteria.

Weighting results are dependent upon the weighting method, that is, the results can be significantly different between models using the same values, but with different weighting methods. The weighting elicitation method must be consistent with the underlying mathematical

[17] Richard Pariseau and Ivar Oswalt "Using Data types and scales" Acquisition Review Quarterly, 1994

models.[18][19][20] Semantic scales and ratio weighting are typically used in an additive preference model.

In semantic scales, all criteria at a given level are compared pair-wise against each other. This is typically done using the Saaty semantic scale[21] by assessing the relative importance of one criteria to another on a 1 (equal importance) to 9 (significantly more important) scale. This method requires each criterion in the pair-wise comparison be carefully defined to ensure the expert is doing the comparison based upon the criterion definition and the overall goal of the model. An axiom of many decision theories (including semantic scales) is that when a new alternative is introduced the rank order of the other criteria does not change. With some implementations of semantic scales, if criteria are added which could be considered a near copy of an existing criterion, rank reversal can occur. This is not a risk if, either the criteria are well defined and there is no interrelation between them prior to weighting, or the semantic scaling is conducted using a multiplicative variant.

Based upon the underlying math of the biosafety risk assessment models, pair-wise comparison using semantic scales was selected as the best possible weighting option. The model was designed to not have interrelated criteria and the criteria were not altered once weighted, eliminating rank reversal issues. Experts were asked to compare the criteria pair-wise within each hierarchy using the Saaty semantic scales. This activity was conducted using a pre-built matrix. The results were then inputted into a commercial software application (Expert Choice ™)[22] which has been designed to convert the Saaty scales into numerical values and use a standard distribution model to combine all expert preferences into a single global weight.

The following figure is one example of the expert weighting results, this figure illustrates the way experts valued the contributions of the criteria for consequences to the overall biosafety risk assessment model (all weights presented in Appendix B):

[18] Paul J.H. Schoemaker and C. Carter Waid, "An Experimental Comparison of Different Approaches to Determining Weights in Additive Utility Models" Management Science, 1982
[19] Paolo Delle Site and Francesco Filiippi, "Weighting methods in Multi-Attribute Assessment of Transport Projects" Eur. Transp. Res. Rev., 2009
[20] Stefan A. Hajkowicz, Geoff T. McDonald, and Phil N. Smith, "An evaluation of multiple objective decision support weighting techniques in natural resources management" Journal of Environmental Planning and Management, 2000
[21] Thomas Saaty, "A scaling method for priorities in hierarchical structures" *Mathematical Psychology*, 1977
[22] http://www.expertchoice.com

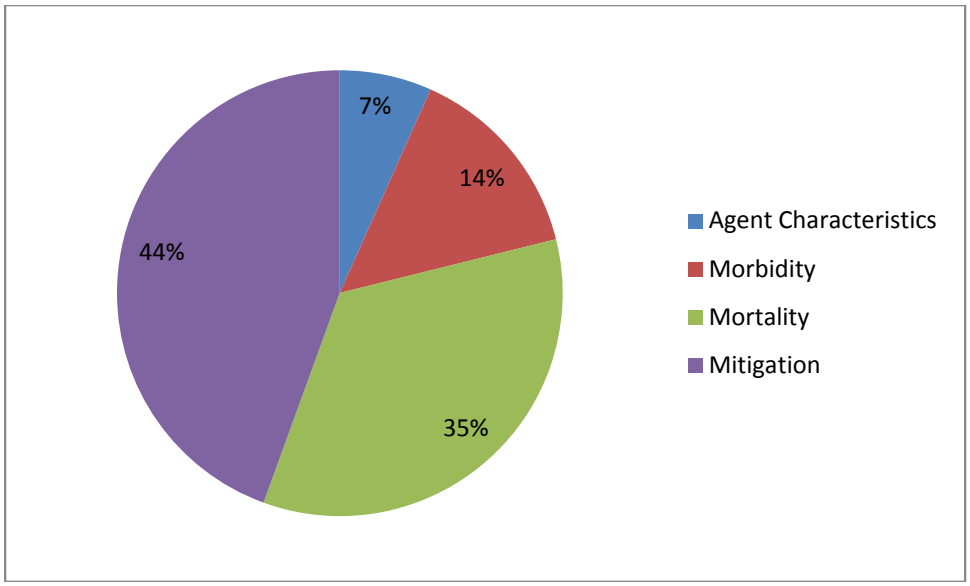

Figure 2: Weights for the Consequences of Disease in Human Host Criteria

Experts were also asked to weigh the "perfect" mitigation measures defined for each exposure route to determine the delta between the defined "perfect" mitigation and judged ability to actually mitigate exposure. In biosafety, there is no perfect mitigation (except for elimination), so implementing mitigation will never completely remove the potential for exposure.

Mitigation measures were valued to be 89% effective at mitigating inhalation exposure to persons inside the laboratory and 99% effective at stopping exposures outside the laboratory. Mitigation measures were valued to be 84% effective at mitigation percutaneous exposure to persons inside the laboratory and 99% effective at stopping exposures outside the laboratory. Mitigation measures were valued to be 89% effective at stopping contact exposures to persons inside the laboratory and 99% effective at stopping exposures outside the laboratory. Mitigation measures were valued to be 94% effective at stopping ingestion exposures to persons inside the laboratory and 99% effective at stopping exposures outside the laboratory.

Calculations

For each model, four specific values were calculated. The first value (L_i) defined the likelihood of infection for a specific route, e.g. the likelihood of infection via inhalation. The second value (L_e) defined the exposure potential for a specific route based upon the procedures, e.g. the likelihood of aerosol exposure. The third value (L_m) defined the level of in-place safety measures for the specific route, e.g. the reduction in aerosol exposure based upon the use of biosafety measures. The fourth value (C) defined the consequence of disease in a host assuming infection and the effectiveness of possible treatment.

The models all use an additive value function to calculate each of the four values; the criteria were first combined with their respected weights by multiplying each criterion value by its weight, then all weighted criteria were summed. To calculate the relative risk for each scenario, the specific likelihood values were then combined to create the overall likelihood score and the consequence score was calculated for each of the "at-risk" hosts.

Likelihood

Likelihood of Exposure To calculate the likelihood of exposure for a specific route, the biosafety risk assessment methodology follows the standard principle that more mitigation the smaller the risk, but the risk can never be zero. First, the model must calculate the mitigation value (L_M); this value is defined as the percent effectiveness of the in-place biosafety measures as compared to "perfect" mitigation. "Perfect" mitigation as defined in the absolute scale is equal to four; no mitigation is defined as zero. To calculate this value, the weighted additive value of all the in-place mitigation measure scores is divided by the "perfect" mitigation value (four). This value is than multiplied by the potential of exposure score (which is the weighted additive value of the defined criteria for the specific exposure route) (L_e) .This determines the overall percent effectiveness of the defined in-place safety measures to mitigate the potential of exposure of the specific route.

$$L_M = (L_m / 4)* L_e$$

The overall likelihood of exposure is then calculated by subtracting the weighted mitigation measure value from the exposure potential value (L_e). The mitigation measure ($W_{m)}$ for each potential exposure route where specifically weighted by biosafety experts to capture the imperfection of mitigation due to such things as human error and equipment failure; these weights define how much mitigation can actually reduce the likelihood, since there is no true perfect mitigation.

$$L_E = L_e – (L_M * W_m)$$

This process allows for more mitigation to make the overall likelihood of exposure very small, but will not allow it to be less than or equal to zero.

Likelihood of infection The likelihood of infection is calculated by an additive value function which combines the weighted criteria.

Overall Likelihood There is a direct relationship between the likelihood of infection (L_i) and the likelihood of exposure, that is, if there is no potential for infection for a given route the potential for exposure via that route is not relevant and inversely if the potential for infection for a given route is very high the potential of exposure for that route is of great important. Therefore, to calculate the overall likelihood these values are combined using a geometric mean.

$$L = \sqrt{} (L_e * L_i)$$

Consequences

The consequences of disease assuming infection are calculated by taking the weighted additive value of all the criteria which define the resulting disease (C_d) and subtracting the weighted additive value of the available consequence mitigation measures (C_m)

$$C = C_d – C_m$$

Risk

Risk is defined as likelihood and consequences. This resulting value of each risk (likelihood and consequences) is displayed using a two-dimensional graph with likelihood on one axis (Y axis) and consequences on the other (X axis) (Figure 3). As demonstrated by Kaplan and Garrick,[23] multiplying the consequences by the likelihood to produce a single risk score does not allow the differentiation between a low likelihood high consequence event and a high likelihood low consequence event in reviewing the results as a quantitatively single value or graphically.

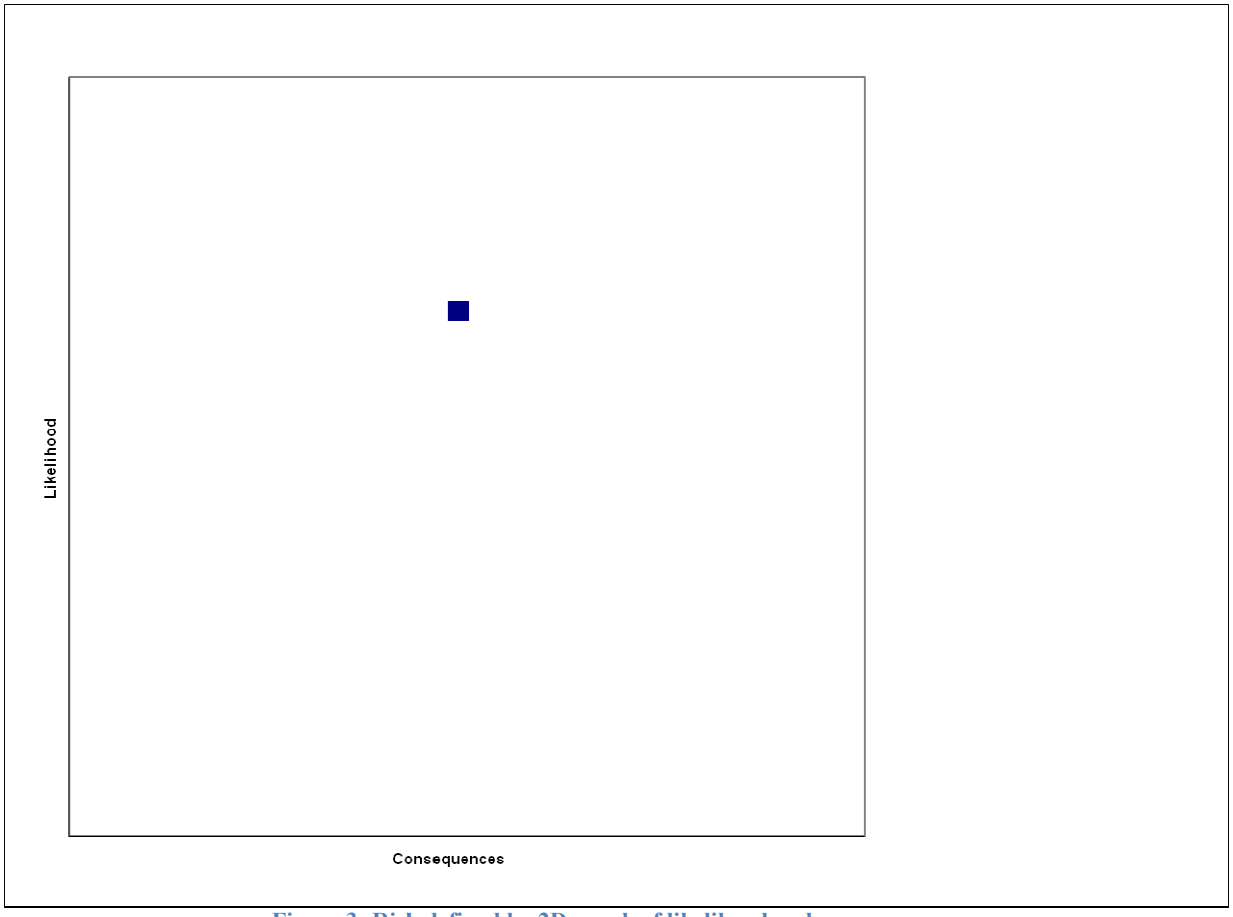

Figure 3: Risk defined by 2D graph of likelihood and consequences

Risk Acceptance

As mentioned previously, this methodology is focused on characterizing the technical risk and presenting a set of relative risks to be used by risk management in evaluating the level of risk acceptance. The risk results can be presented graphically which alone provides a determination on the level of risk. However, the evaluator can create graphical risk acceptance curves which can support relative risk evaluation. The following are a set of example risk acceptance curves.

[23] Stanley Kaplan and B. John Garrick, "On the Quantitative Definition of Risk" Risk Analysis 1981

Using this methodology, likelihood and consequences are typically treated with equal importance. The risk acceptance curves can be set with an equal distribution (Figure 4) between the highest and lowest risks.

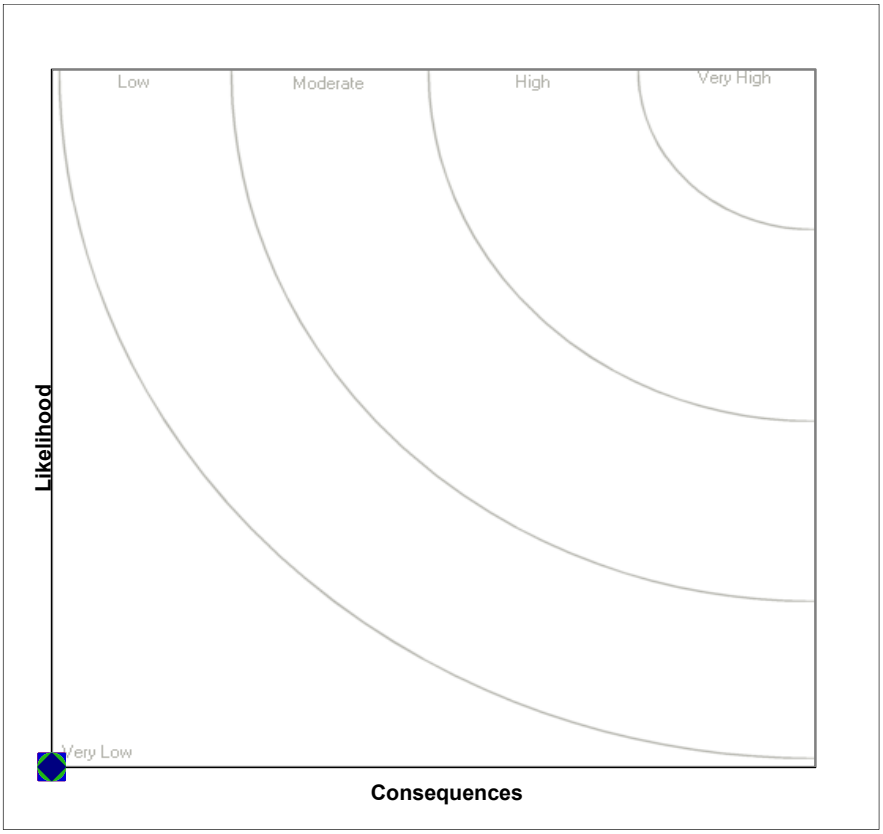

Figure 4: Likelihood and Consequence Graph with Equal Distribution Risk Acceptance Curves

To graphically illustrate a low risk tolerance (Figure 5) or a high risk tolerance (

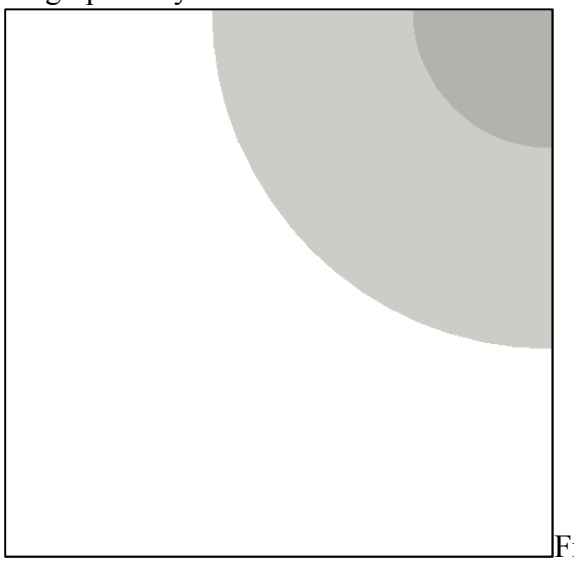

Figure 6), the distance between the risk acceptance curves may be altered to reflect these management positions.

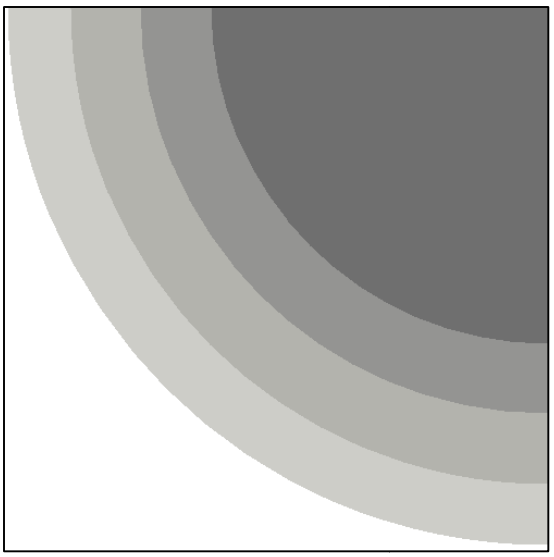

Figure 5: Risk Adverse Acceptance Curves

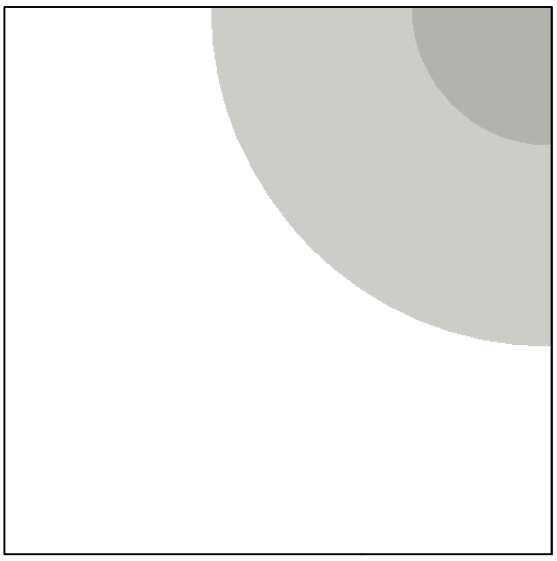

Figure 6: Risk Tolerant Acceptance Curves

Where public concern and risk management are primarily focused on the consequences of disease and less focused on the likelihood of exposure and infection, the risk acceptance curves (Figure 7) can be skewed to reflect this type of risk acceptance. In this case, the highest risks, in the dark grey, are defined by consequences regardless of the level of likelihood.

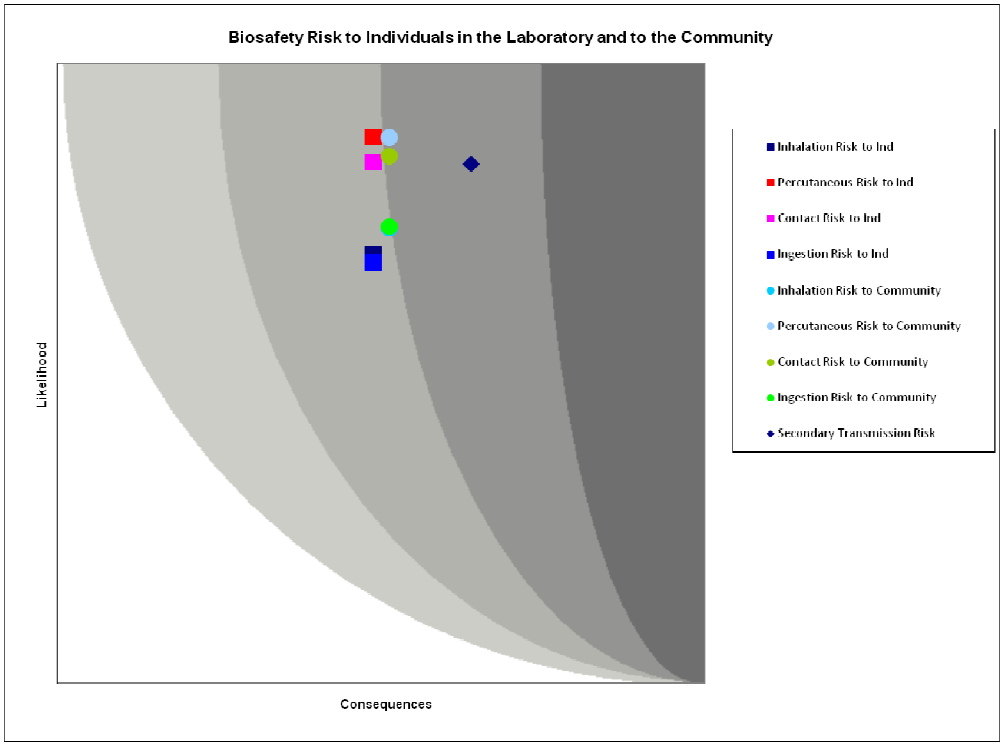

Figure 7: Consequence driven risk acceptance

Validation of the methodology and model

Upon completion of the model, biosafety experts from around the world where asked to participate in the validation process. Model validation methods used were corroboration of model results by other assessment tools (or models) and or critical review conducted by technical specialist, conducted by biosafety experts. Users were asked to conduct risk assessments using the model and compare the results to their expert judgment or to their current assessment processes. Sandia received over 40 detailed assessment results from seven countries: Egypt, India, Switzerland, Germany, the UK, Pakistan, Uganda, and the US. (Users from additional countries also provided back general comments and summaries) Laboratories included in this validation activity included modern research laboratories, research and diagnostic laboratories in developing countries, and diagnostic laboratories with limited capacity.

All users found the assessment results agreed with their professional judgments; most found the methodology of reviewing the thirteen risks separately very useful. Some users felt the level of knowledge required about biological agent was more than needed, however as discussed previously, this knowledge requirement was specifically designed into the model. Most users expressed they would continue to use this model. Some had some additional model and report requests. Some reviewers have independently assessed over 20 agents and laboratory processes already using this model; others have expressed their plans to assess over 60 laboratory processes using this model in the next few months. Excerpts of the reviewer's data and reports are included in Appendix B.

Sandia also conducted several internal validation studies. These studies included a comparison of the results of this model to the current defined risk groups as they are presented by the U.S. National Institutes of Health (NIH)[24]. To conduct this analysis, Sandia used internal expertise to "score" 17 agents which are defined by NIH to be in either risk group 1, 2, 3, or 4. The same likelihood of exposure scores (or laboratory processes) was used to assess the four possible risks to persons working in the laboratory. The worst-case or highest likelihood for each agent was used in this analysis. The results of this study, (Figure 8), did not match the risk groupings completely[25]. However, if the risk acceptance was consequence focused (with four categorizations of risk – High, Moderate, Low, Very Low); there was a direct correlation, with only a few explainable differences, between the Biosafety RAM results and the NIH risk groupings (Figure 9). Detailed results and calculated scores are provided in Appendix C.

> *Burkholderia pseudomallei* fell into the high risk categorization, along with Marburg virus; NIH categorizes this agent as risk group 3. *Burkholderia pseudomallei* was assessed in this model using some recent studies which highlight a significant mortality rate for this disease in otherwise healthy adults; there are also several papers which express a lower mortality rate, for this study the worst case mortality was used. A lower mortality rate would have placed *Burkholderia pseudomallei* with a similar consequence to *Mycobacterium tuberculosis*. Human immunodeficiency virus (HIV) and Yellow

[24] Department of Health and Human Services, *NIH Guidelines for Research involving Recombinant DNA Molecules (NIH Guidelines,)* 2002 (Revised September 2009)

[25] The differences between the default biosafety RAM results and the NIH risk groupings would, for example, place agents like Ebola Zaire and Marburg virus in the same risk group classification and Avian Influenza H5N1 and *Mycobacterium tuberculosis*

fever virus, both NIH risk group 3 agents, fell into the low risk category. The two viral agents were assessed with vaccinations or post-exposure treatments existing and available which dramatically reduced the consequences for both agents; this explains the delta between the NIH classification and the models for these agents. This study highlights that, one, this model provides relative risk differentiation of agents which has a solid biological basis, and, two, NIH risk group classifications are consequence based.

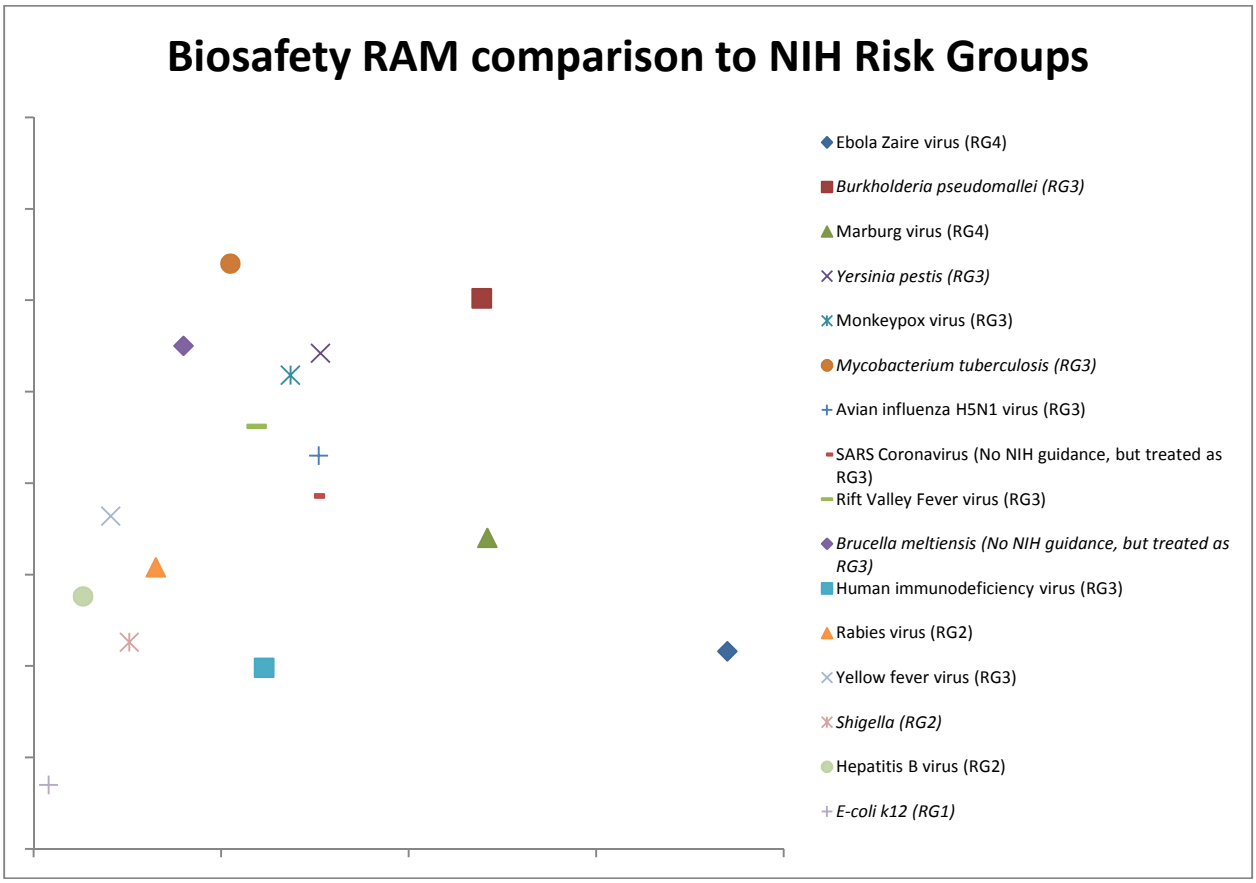

Figure 8: Results of Biosafety RAM assessment of 17 agents

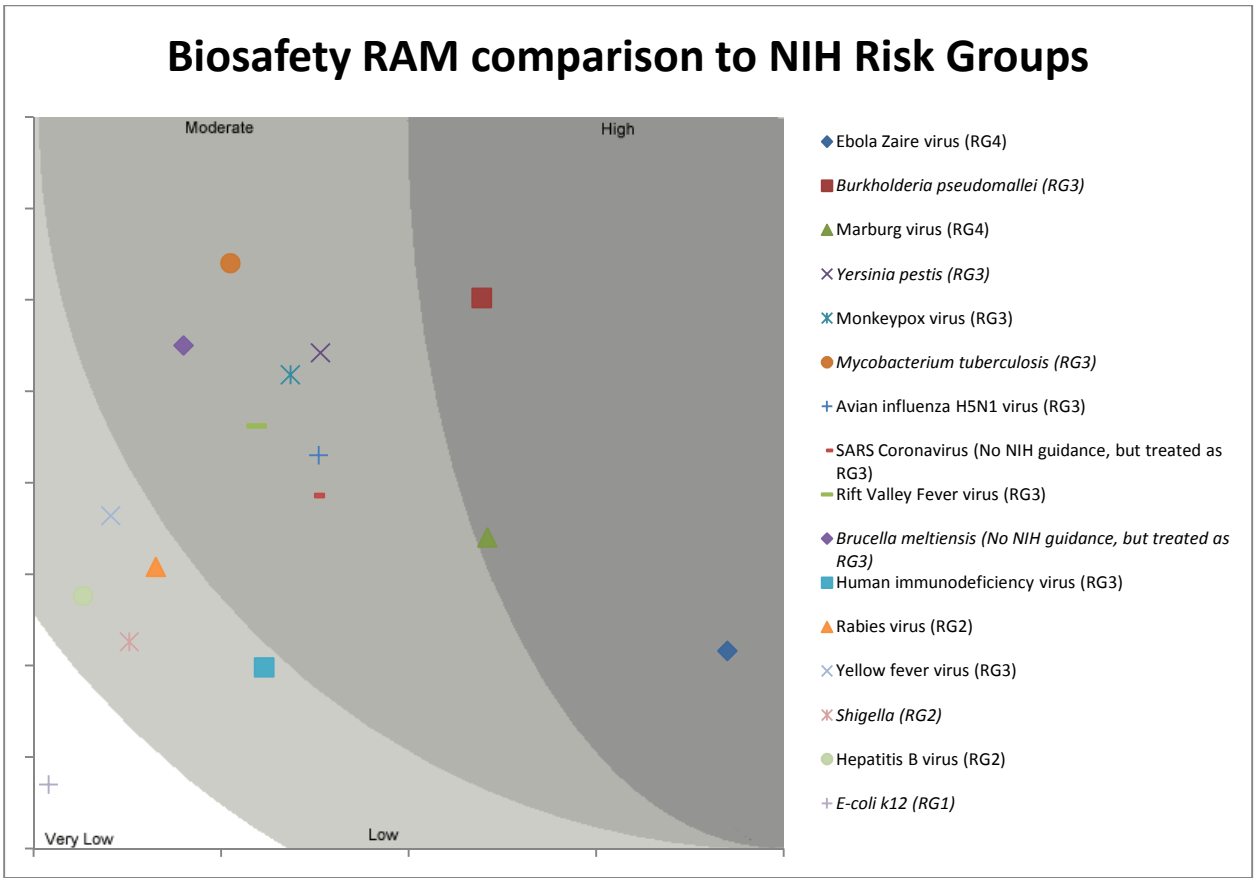

Figure 9: Biosafety RAM modeled agents as compared to NIH risk group classifications

Sandia also conducted validation analysis on the mathematical equations of the model to verify the linear nature of the ratio scales and consistency of the weighted additive value functions. Sandia also verified there were no rank reversals in results due to the weights. Additionally, Sandia created score sensitivity tables which can be used to highlight the risk drivers. This process ensured the mathematical equations used to calculate the mitigated potentials and the overall likelihood and consequence scores provided results which matched biosafety and infectious disease expert opinion.

Software model

The biosafety risk assessment model has been coded into a software package which runs on Microsoft's© .Net Framework[26]. The software, titled BioRAMSoftware.exe (Version 1.0 dated September 2010), is planned to be released open source and discussions have started to freely license the software to organizations including the World Health Organization.

The software allows users to provide the scores for all the criteria in a simple tool by answering a set of questions. The software calculates the risk scores using the algorithms and weights defined in the model and methodology. The software produces a numeric and graphical report with the relative risk rankings for the user. Additionally, the software produces a chart

[26] http://www.microsoft.com/net

identifying impact each question had on the final results. This feature is useful in understanding and communicating the risks, as well as, providing guidance on risk management or mitigation efforts.

The software also allows users to modify wording of questions and the definitions of the scoring scales to better reflect a unique laboratory situation or language differences. Also, users can view and if needed modify the weights.

Assumptions and Limitations

This methodology is not an all hazards assessment of laboratory work, but is limited to those hazards and risks specifically associated with biological materials. The methodology can be expanded and new models created which support additional hazard and risk assessments. For the initial generation of this methodology and the accompanying models, a narrow focus was desirable. Additionally, the models do not specifically support toxins, plant pathogens, or nano-particles; however, the general methodology can be used for these hazards.

Agents are assessed with a single consequence value. For agents which cause multiple diseases, they currently, must be assessed as separate agents (e.g. *B. anthracis* should be assessed separately for the inhalation, cutaneous, and gastrointestinal forms).

The methodology and the models require knowledge about the biological agents in use and the laboratory processes and practices. The models have been designed for use by a biosafety knowledgeable person. This methodology does not define the acceptable level of risk, but presents a relative risk result. The judgment of acceptance must be made as part of the evaluation process and should include management.

Observations

The methodology and models developed in this project met the intended goal of producing a systematic and standardized process for conducting laboratory biosafety risk assessments. The methodology outlined is consistent with internationally accepted risk assessment schemes and also parallels international biosafety risk assessment guidance. For example, the German Guideline for Risk Assessment and for the Instruction of Employees in relation to Activities with Biological Agents[27] lists the following four focal points for the risk assessment:

1. Information regarding the identity, classification and infection potential of the biological agent and the sensitizing and toxic effects (or consequences) emanating from them
2. Activity-related information including procedures and work processes
3. Type and duration of activities
4. Level of users experience, knowledge

The World Health Organization states in the Laboratory Biosafety Manual[3] that a biosafety risk assessment should take into consideration: the biological agent, the facilities available, and the equipment and practices used.

[27] Bundersarbeitsblatt 6-2006, Technical Rules for Biological Agents, *Guildeline for Risk Assessment and for the Instruction of Employees in relation to Activities with Biological Agents,* TRBA 400

Biosafety RAM falls within these generalized definitions of how to conduct a biosafety risk assessment:

Evaluate the biological agents that exist at the facility.
Evaluate the facility processes and procedures.
Evaluate the existing biorisk mitigation measures.

Conclusions

This methodology and accompanying models and tools will provide the structure currently lacking in biosafety risk assessments. The methodology developed in partnership with an international biosafety expert group can provide a framework for discussing biosafety risk assessment broadly. This methodology also complements the methodology developed for assessing laboratory security (or biosecurity) risks and jointly can help support a rugged biorisk management system.

The criteria defined in this model can also help the biosafety community in better understanding the scope of the hazards and risks when reviewing the laboratory environment. The models provide a unique method for evaluating biosafety mitigation measures and may help future laboratories in better defining the mitigation strategies.

The model and the software tool are just starting points and as more of the internationally community uses this tool and provides feedback the model can be strengthened and focused to provide a variety of risk results.

Next Steps

As this methodology and the accompanying models continue to be refined, there are some clear additional activities. Feedback from the continued validation of the methodology and model by laboratories internationally will be used to enhance, and as needed, repair the model.

Also, users have requested the development of a biological agent library which can be used to pre-answer the specific questions about the biological agent. This would allow the user to review and modify the answers as needed, but would provide a more consistent starting point for all laboratories around the world.

Two additional features regarding the modeling of the consequences have also been requested, the first is to have the consequences specifically tied to the routes of infection which would allow for biological agents which can cause multiple diseases to be assessed once rather than independently for each route. Second, the modeling of the consequences would be more accurate if the consequences criteria scores were distributed between worst-case, typical case, and best case. This would allow for a more accurate representation of the different consequences to humans and animals than are currently presented.

Appendix A – Scoring Tables for all criteria

Agent factors which impact the biosafety risks to humans
Is this agent known to cause infection via inhalation in humans (to cause infection via droplets or droplet nuclei that have entered the upper or lower respiratory tract) in a laboratory setting? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
Is this agent known to cause infection via inhalation in humans (to cause infection via droplets or droplet nuclei that have entered the upper or lower respiratory tract) in the natural environment? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown in humans? 4 = Yes 2 = No 0 = If this is not an infectious route
Is this agent known to cause infection via percutaneous exposure in humans (to cause infection through compromised skin or direct injection into the blood stream) in a laboratory setting? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
Is this agent known to cause infection via percutaneous exposure in humans (to cause infection through compromised skin or direct injection into the blood stream) in the natural environment? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown in humans? 4 = Yes 2 = No 0 = If this is not an infectious route
Is this agent known to cause infection via direct contact in humans (to cause infection through the mucosal membranes) in a laboratory setting? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route

Is this agent known to cause infection via direct contact in humans (to cause infection through the mucosal membranes) in the natural environment?
4 = Preferred Route
2 = A possible route
1 = Unknown
0 = Not a route

Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown in humans?
4 = Yes
2 = No
0 = If this is not an infectious route

Is this agent known to cause infection via ingestion in humans (to cause infection via contact with the gastrointestinal tract) in a laboratory setting?
4 = Preferred Route
2 = A possible route
1 = Unknown
0 = Not a route

Is this agent known to cause infection via ingestion in humans (to cause infection via contact with the gastrointestinal tract) in the natural environment?
4 = Preferred Route
2 = A possible route
1 = Unknown
0 = Not a route

Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown in humans?
4 = Yes
2 = No
0 = If this is not an infectious route

Is this agent known to cause infection via vector-borne transmission in humans (to cause infection by direct mucosal membrane contact or percutaneous exposure from a vector (e.g. arthropod))?
4 = Preferred Route
2 = A possible route
1 = Unknown
0 = Not a route

Is this agent known to cause infection via vertical transmission in humans (to cause infection from mother to fetus in the womb or via ingestion of infected breast milk)?
4 = Preferred Route
2 = A possible route
1 = Unknown
0 = Not a route

Is this agent known to cause infection via sexual transmission in humans (to cause infection through sexual contact including intercourse)?
4 = Preferred Route
2 = A possible route
1 = Unknown
0 = Not a route

What is this agent's stability outside of a host? 1 = Agent not stable outside the host 2 = Agent stable on interior surfaces for days to weeks 3 = Agent stable in the exterior environment for days to weeks 4 = Agent stable in the environment for months
How easily does this agent transmit between human hosts? 4 = Agent can easily transmit between human hosts 2 = Agent is transmissible between human hosts via close contact only (direct fluid transmission between hosts) 2 = Human to human transmission suspected 0 = Human to human transmission has never been demonstrated
How easily does this agent transmit from animal to human hosts? 4 = Agent can easily transmit from animals to humans 2 = Agent is transmissible from animals to human hosts via close contact only (direct fluid transmission between hosts) 2 = Animal to human transmission suspected 0 = Animal to human transmission has never been demonstrated
How easily does this agent transmit from human to animal hosts? 4 = Agent can easily transmit from humans to animals 2 = Agent is transmissible from humans to animals via close contact only (direct fluid transmission between hosts) 2 = Human to animal transmission suspected 0 = Human to animal transmission has never been demonstrated
Does this agent or one of its by-products cause a carcinogenic or mutagenic reaction in a human host? 4 = Yes 2 = Unknown 0 = No
Does this agent have toxin or enzyme production which has a negative impact in a healthy human host? 4 = Yes 2 = Unknown 0 = No
Does this agent suppress a human host's immune system? (E.g. cause dramatic suppression which renders the host unable to respond to other infections) 4 = Yes 2 = Unknown 0 = No
Does this agent have the ability to alter once in a host or in the natural environment to become infectious through new route or new hosts, or to cause increased consequences? 4 = Yes 2 = Unknown 0 = No
What is the duration of illness (the average length of time of clinical signs of infection) in a normally healthy human host? 4 = long duration (months or more) 3 = moderate duration (week(s)) 1 = short duration (days) 0 = No signs of infection

What is the severity of illness (the average severity of illness, ranging from no signs of illness to hospitalized in critical condition) in a normal health human host? 4 = Extreme sign of disease (mechanical assistance required to sustain life or death imminent) 3 = High sign of disease (not able to function (hospitalized)) 2 = Moderate sign of disease (able to function in a limited manner (bed rest)) 1 = Low sign of disease (able to function but showing symptoms) 0 = No sign of disease
What is the duration of infection (the length of time the host is infected with the organism) in a normal healthy human host? 4 = Infection present for life of host 3 = Infection present post clinical signs for months 2 = Infection present post clinical signs for weeks 1 = Infection present if clinical signs 0 = No sign of disease
Does this disease cause any long-term conditions (sequelae) in a normal healthy human host? 4 = High long-term impact which renders the host unable to function normally 2 = Moderate long-term impact which hinders the hosts ability to function normally 1 = Mild long-term impacts do not impede the hosts ability to function normally 0 = No long term impact
What is the frequency of death in humans caused by this disease in a defined population during a specified interval of time (Mortality Rate)? 4 = High mortality (75% or more) 2 = Medium mortality (15% to 74%) 1 = Low mortality (1% to 14%) 0 = No Mortality (0%)
What level of national or international reporting is required for outbreaks of this disease? 4 = Internationally Reportable 2 = Nationally Reportable 0 = Not Reportable
Do effective diagnostic tests exist for humans? 0 = No 2 = Unknown 4 = Yes
Do post exposure treatments (including immuno-globulin, vaccines and anti-microbials) exist for humans? 0 = None exist 2 = Exist, but are only considered partially effective 4 = Effective post exposure treatments exist
Do preventative measures (vaccines) exist for humans? 0 = No preventative measures exist 2 = Exist, but are only considered partially effective (will not prevent but will limit the impact of the disease) or (are only effective in a small population) 4 = Effective preventative measures exits

Agent factors which impact the biosafety risks to animals
Is this agent known to cause infection via inhalation to animal hosts (to cause infection via droplets or droplet nuclei that have entered the upper or lower respiratory tract)? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown in the animal host? 4 = Yes 2 = No 0 = If this is not an infectious route
Is this agent known to cause infection via percutaneous exposure in an animal host (to cause infection through compromised skin or direct injection into the blood stream)? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown in an animal host? 4 = Yes 2 = No 0 = If this is not an infectious route
Is this agent known to cause infection via direct contact in an animal host (to cause infection through the mucosal membranes)? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown in an animal host? 4 = Yes 2 = No 0 = If this is not an infectious route
Is this agent known to cause infection via ingestion in an animal host (to cause infection via contact with the gastrointestinal tract)? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown in an animal host? 4 = Yes 2 = No 0 = If this is not an infectious route

Is this agent known to cause infection via vector-borne transmission (to cause infection by direct mucosal membrane contact or percutaneous exposure from a vector (e.g. arthropod))? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
Is this agent known to cause infection via vertical transmission in an animal host (to cause infection from mother to fetus in the womb or via ingestion of infected breast milk)? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
Is this agent known to cause infection via sexual transmission in an animal host (to cause infection through sexual contact including intercourse)? 4 = Preferred Route 2 = A possible route 1 = Unknown 0 = Not a route
What is this agent's stability outside of a host? 1 = Agent not stable outside the host 2 = Agent stable on interior surfaces for days to weeks 3 = Agent stable in the exterior environment for days to weeks 4 = Agent stable in the environment for months
How easily does this agent transmit from animal to human hosts? 4 = Agent can easily transmit from animals to humans 2 = Agent is transmissible from animals to human hosts via close contact only (direct fluid transmission between hosts) 2 = Animal to human transmission suspected 0 = Animal to human transmission has never been demonstrated
How easily does this agent transmit from human to animal hosts? 4 = Agent can easily transmit from humans to animals 2 = Agent is transmissible from humans to animals via close contact only (direct fluid transmission between hosts) 2 = Human to animal transmission suspected 0 = Human to animal transmission has never been demonstrated
How easily does this agent transmit between animal hosts? 4 = Agent can easily transmit between animal hosts 2 = Agent is transmissible between animal hosts via close contact only (direct fluid transmission between hosts) 2 = Animal to animal transmission suspected 0 = Animal to animal transmission has never been demonstrated
What level of national or international reporting is required for outbreaks of this disease? 4 = Internationally Reportable 2 = Nationally Reportable 0 = Not Reportable

If the agent infects animals, what is the expected morbidity rate to a naïve but otherwise healthy animal population? 4 = High Morbidity (> 75%) 3 = Moderate Morbidity (25% to 75%) 1 = Low Morbidity (1% to 25%) 0 = Very Low Morbidity (< 1%)
What species of animals can this agent infect? 4 = Affects multiple, significant agricultural species which are used for export and/or the by-products are a major source of protein for our country 3 = Affects a single but significant livestock species which is used for export and/or the by-products are a major source of protein for our country 2 = Affects a less significant livestock species which is used for export and/or the by-products are a source of protein for our country 0 = Affect a livestock species which has no economic impact in our country
Do effective diagnostic tests exist for animals? 0 = No 2 = Unknown 4 = Yes
Do post exposure treatments (including immuno-globulin, vaccines and anti-microbials) exist for animals? 0 = None exist 2 = Exist, but are only considered partially effective 4 = Effective post exposure treatments exist
Do preventative measures (vaccines) exist for animals? 0 = No preventative measures exist 2 = Exist, but are only considered partially effective (will not prevent but will limit the impact of the disease) or (are only effective in a small population) 4 = Effective preventative measures exits

Procedures and Processes used for the procedure being assessed
What type of material will be used in this procedure? (If the procedure will have both purified material and diagnostic samples, select the purified material option) 4 = Purified biological materials 2 = Diagnostic samples (e.g. blood, urine, tissue, saliva, etc) 1 = Environmental samples (e.g. soil, water, etc)
What is the greatest volume of material existing at one time in the procedure? 4 = Over 10 liters 2 = Up to 10 liters 1 = Milliliter volume
What is the potential for aerosols to be generated as a byproduct of this procedure (e.g. pipetting, sonication, etc.)? 4 = A notable potential for the generation of aerosols may be produced 1 = A limited quantity of aerosols may be produced 0 = No procedures in use which may generate an aerosol
Are aerosolization experiments being conducted as part of this procedure? 4 = Large scale aerosolization experiments are being performed 3 = Small scale aerosolization experiments are being performed 0 = No aerosol experiments are being performed

What is the potential and extent of a splash or spill in this procedure? 4 = There is a potential for a high pressure sustained release of infectious material 3 = There is a potential for a spill or splash of infectious material 0 = Material does not exist in a spill-able form in the laboratory
How is contaminated waste stored in the laboratory? 4 = Contaminated waste is not stored properly (using standard containers) and is not handled according to best practices. 1 = Contaminated waste is stored properly and handled according to best practices 0 = There is no contaminated waste in laboratory
What is the amount of sharps used in this procedure? 4 = A large volume of sharps in use (e.g. scalpels or needles in use at least daily in this procedure) 3 = A small volume of sharps in use (e.g. scalpels or needles rarely used for this procedure) 0 = There are no sharps in use
What is the amount of breakable material or items with sharp edges in this laboratory? 4 = A large amount of breakable material (e.g. glassware common in laboratory) 3 = A small amount of breakable material 0 = There is no breakable material in the laboratory
How easy are the surfaces in the laboratory to decontaminate? 4 = Surfaces are very difficult to decontaminate (e.g. wood, grout, etc) 2 = Some surfaces are difficult to decontaminate (e.g. edges) 0 = All surfaces can be decontaminated
How is sharp waste handled? 4 = No sharp material ever leaves this laboratory 3 = Sharp waste is first decontaminated and then leaves the facility in puncture-resistant containers 1 = Sharp waste is first decontaminated and leaves the facility in non-puncture-resistant waste containers (e.g. plastic bags) 0 = Sharp waste is removed from the facility prior to decontamination
How is contaminated waste handled? 0 = Contaminated waste is safely and efficiently treated within lab 1 = Contaminated waste leaves lab for external treatment 4 = Contaminated waste is removed from lab and not treated
How is liquid waste (effluent) handled? 0 = Liquid waste is safely and efficiently treated within lab 1 = Liquid waste leaves lab for external treatment 4 = Liquid waste is removed from lab and not treated
Are measures in place to reduce infectious aerosols exiting the laboratory? 4 = All air exhausted from this laboratory is via well-maintained HEPA filters 3 = All air exhausted from this laboratory is via duct work which is not recirculated into other space 2 = All laboratory air is not recirculated, but not specifically exhausted via ducts 0 = Laboratory air is potentially circulated into other facility or community space
Are Biosafety cabinets used in this procedure? 0 = Biosafety cabinets are not in use or not in existence 1 = Biosafety cabinets exist, but are used only periodically - and/or 1 = Biosafety cabinets exist, but no formal training programs or procedures are in place for their use - and/or 1 = Biosafety cabinets exist, but they are not validated/certified on a regular basis (ideally, annually) 4 = Biosafety cabinets are always used, they are routinely validated/certified, well- maintained, and there are procedures in place for proper use

Is all the equipment used in this procedure with a potential to generate infectious aerosols (e.g. centrifuge, vortexer, sonicator) isolated or sealed in a manner to prevent aerosol escape (e.g. sealed rotor cups, equipment in BSC or in a biobubble, etc) prior to use?
0 = Equipment is located and used on an open bench or in an open area and has no internal sealing mechanisms
1 = Equipment is used in isolation or is internally sealed (e.g. used in a BSC, equipment uses sealed rotor cups, etc), but there are no formal procedures for use - and/or
1 = Equipment is used in isolation (e.g. used in a BSC) or is internally sealed, but the mechanism has not been validated or certified
4 = Equipment is always isolated/sealed and devices are validated/certified and well- maintained
(Please leave blank if there is no aerosol-generating equipment in use for this procedure/laboratory)

Are other forms of Primary Containment used in this procedure?
0 = No primary containment devices are used for this procedure
1 = Primary containment devices exist, but are used only periodically - and/or
1 = Primary containment devices exist, but there is no formal training program or procedures in place for their use - and/or
1 = Primary containment devices exist, but they are not validated/certified on a regular basis
4 = Primary containment devices are always used in this procedure, are validated/certified, well-maintained, and there are procedures in place for proper use

Is respiratory protection used in this procedure? (surgical masks are not considered respiratory protection)
0= No respiratory protection exists or is in use
1 = Respirators (e.g. N95, N100, PAPR, Positive Pressure Suit, etc) are used (sometimes, often?) but there is no formal respiratory protection program (standardized fit testing or training) in place prior to use
4 = Respirators are (always?) used and there is a formal respiratory protection/training program in place prior to use

What types of gloves are in use while using sharps (e.g. needles, scalpels, etc) in this procedure?
0 = No gloves are typically worn while handling sharps
0 = A single pair of latex or nitrile type gloves are typically worn while handling sharps
1 = Two pairs of latex or nitrile type gloves are typically worn while handling sharps
4 = Heavy gloves (e.g. leather or thick rubber gloves) are typically worn while handling sharps

What types of gloves are used for this procedure?
0 = Gloves are not typically worn
3 = A single or double pair of latex or nitrile type gloves are worn during the duration of the procedure
4 = A single or double pairs of latex or nitrile type gloves are worn and the outer most pair is changed after handing contaminated or potentially contaminated objects

What type of protective clothing (PPE) is used in this laboratory?
0 = Personnel wear street clothes in the laboratory and typically do not use gowns or lab coats.
3 = Gowns or lab coats are always worn over street clothes
4 = Personnel wear dedicated laboratory clothing (e.g. scrubs) which is not worn outside the laboratory, anteroom, or change room

What type of protective eyewear is used in this laboratory?
0 = No eyewear protection is typically used
1 = Personnel wear safety glasses
3 = Personnel wear goggles **or** a face shield
4 = Personnel wear goggles **and** a face shield

What types of shoes are worn in the laboratory?
0 = Persons can wear open-toe shoes in the laboratory
1 = Persons must wear closed-toed shoes
2 = Solid shoes are worn
3 = Shoe covers are worn over solid shoes, shoe covers are not worn outside laboratory, anteroom, or change room
4 = Laboratory-dedicated solid shoes are worn, shoes are never worn outside laboratory, anteroom, or change room

Are face shields or masks worn for this procedure? 0 = Personnel do not wear any face protection 3 = Surgical masks are used to protect mouth/nose from contact 4 = Face shields are always used to protect the eyes/mouth/nose from contact
Does this laboratory have procedures in place for agent handling to reduce/eliminate aerosols? These procedures should meet defined best practices 0 = Personnel are not specifically trained how to minimize the production of aerosols 1 = Proper practices for reducing/eliminating aerosols exist, but are not taught, enforced, verified, or documented 4 = Proper practices for reducing/eliminating aerosols are identified in the laboratory procedures, are taught, and verified on a regular schedule
Are absorbent materials used on the bench or BSC to contain spills and reduce splashing? 0 = Absorbent material is never used 0 = Absorbent material is used on the bench or BSC but only replaced periodically 1 = Absorbent material is sometimes used 4 = Absorbent material is used for all procedures (on the bench or BSC) and disposed of after each use
After working with potentially contaminated material (cultures, infectious waste), how are objects that should not become contaminated (door handles, computer keyboards) handled? 0 = Hands are never decontaminated prior to handling "Clean" objects 4 = Hands are always decontaminated prior to handling "Clean" objects
How frequently are hands washed? 0 = No formal hand washing policies exist 2 = Hands are washed only when leaving the lab 4 = Hands are always washed frequently during the procedure (e.g. hands are washed between each procedure step)
How are sharps handled in the laboratory? 0 = Sharps are always handled by hand 2 = Sharps are rarely handled by hand 4 = Sharps are never handled by hand directly (e.g. needles are not recapped, a mechanical system like forceps are used to remove needles and/or scalpel blades, etc)
Does this laboratory have procedures in place for spill response that meet defined best practices? 0 = The laboratory does not have spill response procedures in place 2 = The lab has basic spill response procedures in place, but does not conduct validation exercises on these procedures 4 = The lab has validated and exercised spill response procedures, including spill response kits (which contain appropriate PPE, cleaning items, and other required items), training on spill response, plans for validation of spill cleanup, spill response SOPs, and spill response decontamination mechanisms including waste validation.
Does this laboratory have procedures in place for lab workers to reduce/eliminate contact exposure through broken skin that meet defined best practices? 0 = No procedures exist to reduce/eliminate contact exposure through broken skin 1 = Proper practices for reducing/eliminating contact exposure through broken skin exist, but are not taught, enforced, verified or documented 4 = Proper practices for reducing/eliminating contact exposure through broken skin are identified in the laboratory procedures and are taught and verified on a regular basis
Does this laboratory have procedures in place for sharps handling to reduce/eliminate percutaneous exposure that meet defined best practices? 0 = Personnel are not specifically trained how to minimize percutaneous exposures 1 = Proper practices for reducing percutaneous exposure exist. but are not taught, enforced, verified or documented 4 = Proper practices for reducing percutaneous exposure are identified in the laboratory procedures, are taught, and verified on a regular schedule

What is the implemented process for the decontamination of equipment prior to maintenance? 4 = There is no decontamination of equipment prior to maintenance or repair 3 = Decontamination of equipment prior to maintenance or repair is performed, but not validated 0 = No equipment is maintained or repaired without decontamination, and the process is documented and validated
Are all biological agents in this laboratory inventoried? 0 = There is no inventory system at this laboratory 1 = This laboratory has a limited inventory system 4 = This laboratory has a complete and well-maintained inventory system
Is there a shipping and receiving program in place at this laboratory? 0 = There is no shipping and receiving program at this laboratory 1 = This laboratory has limited procedures in place for shipping and receiving 2 = This laboratory has some procedures in place for shipping and receiving, but lacks oversight in implementation 4 = This laboratory has an active shipping and receiving program, and well-defined procedures and plans in place
Are there procedures in place to ensure that the species and strain of the laboratory agents are correct? 0 = This laboratory does not verify agents 1 = This laboratory has limited procedures in place for verifying agents 2 = This laboratory has some procedures in place for verifying agents, but lacks oversight in implementation 4 = This laboratory has an active verification program, and well-defined procedures and plans in place
Are there procedures in place for preventative equipment maintenance to reduce/eliminate accidents or equipment failure, which meet defined best practices? These would include equipment calibration, validation, certification, etc. 0 = There is no equipment maintenance program at this laboratory 1 = This laboratory has limited procedures in place for equipment maintenance, but maintenance is generally reactive rather than preventative 2 = This laboratory has some procedures in place for maintenance, but lacks oversight in implementation 4 = This laboratory has an active preventative equipment maintenance program, and well-defined procedures and plans in place
Is there a Medical Surveillance program in place? 0 = There is no medical surveillance at this laboratory 1 = This laboratory has limited procedures in place for medical surveillance 2 = This laboratory has some procedures in place for medical surveillance, but lacks oversight in implementation 4 = This laboratory has an active medical surveillance program, and well-defined procedures and plans in place
Are there standard operating procedures in place for unexpected or catastrophic incidents, including the release of or exposure to an infectious agent (e.g. Incident response plans)? 0 = There is no incident response program at this laboratory 1 = This laboratory has limited procedures in place for incident response, but maintenance is generally reactive rather than preventative 2 = This laboratory has some procedures in place for incident respons, but lacks oversight in implementation 4 = This laboratory has an active incident response program, and well-defined procedures and plans in place
Is there a formal personal protective equipment (PPE) program in place? 0 = There is no PPE program at this laboratory 1 = This laboratory has a limited PPE program in place 2 = This laboratory has some procedures in place for PPE, but lacks oversight in implementation 4 = This laboratory has an active PPE program which includes, well-defined procedures for donning, doffing, storing, and maintaining PPE

Does this laboratory implement standard good laboratory practices for safety? 0 = This laboratory does not have established procedures in place which includes standard good laboratory practices 1 = This laboratory has limited established procedures in place which include standard good laboratory practices 2 = This laboratory has some procedures in place which include standard good laboratory practices, but lacks oversight in implementation 4 = This laboratory has an active good laboratory practice program and well-defined procedures that employees are familiar with and implement
Are there defined procedures in place for entry into the laboratory? 0 = There are no defined access control procedures in place for this laboratory 1 = This laboratory has limited procedures in place for access control 2 = This laboratory has some procedures in place for access control, but lacks oversight in implementation 4 = This laboratory has a comprehensive access control program, well-defined procedures to determine who can enter the laboratory, including personnel and visitors, and how these decisions will be enforced
Is there a waste and decontamination program in place? 0 = There is no waste management and decontamination program at this laboratory 1 = This laboratory has limited procedures in place for waste management and decontamination 2 = This laboratory has some procedures in place for waste management and decontamination, but lacks oversight in implementation 4 = This laboratory has a comprehensive waste management and decontamination program, and well-defined procedures in place
Does the institution have defined roles and responsibilities for biosafety? 0 = There is no identification of, or education on, biosafety roles and responsibilities 2 = Facility personnel are educated on their biosafety roles and responsibilities 3 = A biosafety officer is identified at this facility 4 = Management at this facility ensures roles, responsibilities, and authorities are defined, documented, and communicated
Has the institution made a commitment to safety? 0 = Management at this facility is not aware, or interested in, biosafety concerns 1 = Management at this facility is aware of biosafety concerns, but has not implemented a biosafety policy or devoted resources to address the issue 2 = Management at this facility have made some efforts to improve biosafety at the facility, but they are not comprehensive and/or are not fully implemented 3 = This facility has a comprehensive biosafety policy in place, which was developed, authorized, and signed by top management. The policy is appropriate to the nature and scale of the risk. Management establishes the commitment and objectives of the biosafety system, and communicates this to all stakeholders. 4 = Management at this facility identifies and prioritizes program needs and allocates funds as necessary
Does the institution have comprehensive biosafety documentation? 0 = This facility has no biosafety policies, manuals, or SOPs 1 = This facility has no specific biosafety documentation 2 = This facility has some biosafety documentation, but they are not comprehensive and / or not fully implemented 3 = This facility has biosafety policies, manuals, and SOPs 4 = This facility's biosafety documentation also includes risk assessment and incident response information
Does the institution conduct biosafety drills or exercises? 0 = This facility does not conduct any biosafety exercises 1 = This facility conducts tabletops or other exercises on an ad hoc basis 2 = This facility conducts annual exercises 4 = This facility includes external responders in their exercises

Does the institution periodically review the biosafety program?
0 = There is no review of the biosafety program
1 = The biosafety program is reviewed and revised as necessary after any incidents or near-incidents
3 = The biosafety program is subject to internal self-assessments
4 = Management at the facility ensures continual improvement, conducts routine self- assessments, and ensures corrective and preventive actions. Reviews include assessing opportunities for improvement and any needs for changes to the system, procedures, policies, and objectives.

Procedures and Processes involving animals used for the procedure being assessed
How many animals are in use in this procedure? 4 = A large number of animals exist in the laboratory (e.g. more than 50 small animals or rodents, or more than 5 larger animals) 3 = A small number of animals exist in the laboratory (e.g. less than 50 small animals or rodents, or less than 5 larger animals) 0 = There are no animals in the laboratory
What is the typical size of these animals? 4 = Large animals (> 15 lbs) 3 = Medium animals (5 to 15 lbs) 3 = Arthropods 1 = Small animals (< 5lbs) 0 = There are no animals in the laboratory
Are there more than one species of animal in use in the laboratory? 4 = More than 2 different species in use 2 = Only 2 species of animals in use 1 = Only 1 species of animal in use this laboratory during the duration of this procedure 0 = There are no animals in the laboratory
Are animals which have the potential to shed infectious particles used in this procedure? 0 = There are no animals in this laboratory 3 = Animals are used, but not expected to shed infectious particles 4 = Animals are used and can shed infectious particles (via sneezing, coughing, in saliva, in skin lesions, in urine, in feces, etc.)
Are animals which have the potential to bite or scratch (transmit infectious material through the skin) used in this procedure? 4 = The animals are naturally highly aggressive (non-human primate) 3 = The animals are docile, but is capable of puncturing skin, if provoked (e.g. cat, dog, ferret) 3 = The animals are arthropods which can serve as a vector for the agent(s) in use in this procedure 1 = The animals used are not typically able to puncture skin 0 = There are no animals in the laboratory
How much waste does the laboratory animals used in this procedure generate? 4 = The animals generate large quantities of animal by-products/waste 3 = The animals generate small quantities of animal by-products/waste 0 = There are no animal by-products in the laboratory
Are sharps handled while working with the animals used in this procedure? 4 = Sharps are regularly used while handling the animals 3 = Sharps are rarely used while handling the animals 0 = There are no sharps in use while handling the animals or animals required for this procedure

Are animals housed in a manner that is isolated or sealed to prevent aerosol escape (e.g. isolator cages or cages inside a biobubble)? 0 = Animals are housed in cages which are located in an open area and have no internal sealing/air filtering mechanism 1 = Animals are housed in some form of isolator, but there are no formal procedures in place for its use 1 = Animals are housed in some form of isolator, but the isolator is not regularly validated/certified. 4 = Animals are housed in isolated or self-contained air-isolating devices which are validated/certified and well-maintained
Are animals handled in isolation to prevent aerosol escape (e.g. in a BSC or handled inside a biobubble)? 0 = Animals are handled in an open area 1 = Animals are handled in some form of isolator, but there are no formal procedures in place for its use 1 = Animals are handled in some form of isolator, but the isolator is not regularly validated/certified. 4 = Animals are always handled in an air-isolating device (e.g. BSC) which is validated/certified and well-maintained
Are animals transported in a manner that prevents aerosol escape (e.g. isolator cages)? 0 = Animals are transported in open cages or no cages 1 = Animals are transported in some form of isolator, but there are no formal procedures in place for its use 1 = Animals are transported in some form of isolator, but the isolator is not regularly validated/certified. 4 = Animals are transported in isolated or self-contained air-isolating devices which are validated/certified and well-maintained
How are animals handled in the laboratory? 0 = Animals are handled by hand 2 = Animals are rarely handled by hand, only when absolutely necessary 3 = Animals are only handled by hand when anesthetized 4 = Animals are never handled directly by hand (mechanical restraining systems or isolation systems are always used)
Does this laboratory have animal handling procedures in place to reduce/eliminate exposures, which meet defined best practices? 0 = Personnel are not specifically trained/taught how to minimize animal handling exposures 1 = Proper practices for animal handling exist, but they are not taught, enforced, verified or documented 4 = Proper practices for animal handling are identified in the laboratory procedures, are taught, and verified on a regular basis
How are animals disposed of post-procedure? 0 = Animals are disposed of safely and efficiently in the lab or adjoining space (e.g. incinerated, digested, or rendered onsite) or no animals exist 1 = Animals are disposed of safely and efficiently outside the laboratory (e.g. incinerated by a third party) 4 = Animals are removed from the lab and are not treated (e.g. buried or sent to local land fill)
Are measures in place to reduce the potential/likelihood of an animal escaping from the laboratory? 0 = There are no animals in this laboratory 1 = This laboratory has been designed to best practices to reduce the potential/likelihood of an animal escaping 4 = There are no specific laboratory measures in place to reduce the likelihood/potential of an animal escaping

Appendix B– Expert Weighting Summary

Likelihood of Infection

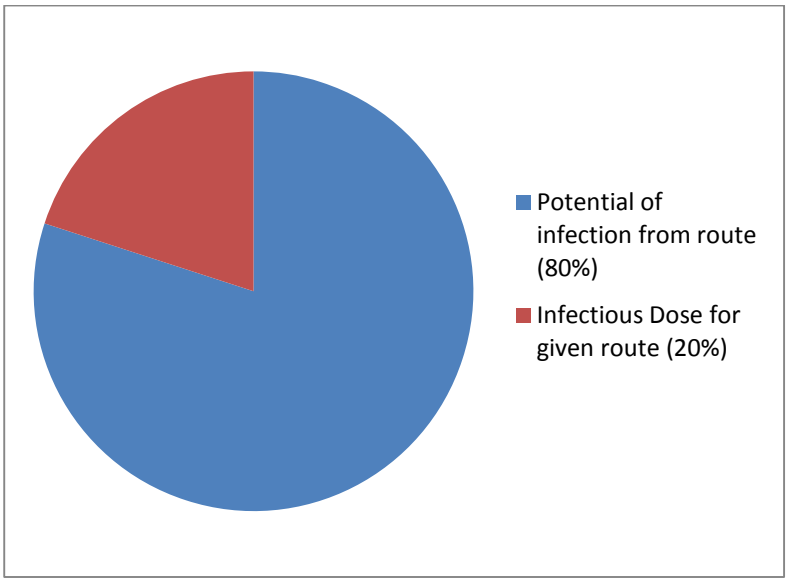

Figure 10: Weights of Likelihood of infection for all routes

Likelihood of Inhalation Exposure

Likelihood of inhalation Exposure to Individuals inside of Laboratory

		Weights
Type of Material		
	Quality	8.38%
	Quantity	3.10%
Inhalation Exposure		
	Accidental Aerosol	22.14%
	Aerosol Experiment	24.60%
	Spill	14.76%
Decontamination of Equipment		9.02%
Animals		
Quality of Animals		
	Number	4.50%
	Size	4.50%

Multiple Species	3.06%
Shedding	2.97%
Waste	2.97%
Exposure Mitigation	
Containment	28.90%
PPE	
Respirators	15.30%
Procedures	
Handling	12.75%
Standard Procedures	
Inventory	0.10%
Strain ID	0.11%
Equip Maintenance	0.34%
Incident Response Plans	0.26%
PPE Program	0.19%
GLP	0.20%
Management	
Roles and responsibilities	1.65%
Commitment	0.59%
Documentation	0.26%
Drills	0.26%
Review	0.53%
Animals	
Housed	7.01%
Manipulated	7.01%
Transported	7.01%
Handled	7.01%

Likelihood of Exposure to community outside the laboratory

	Weights
Type of Material	
Quality	10%
Quantity	4%
Inhalation Exposure	
Aerosol Generation	86%
Exposure Mitigation	
Secondary Containment (Exhaust)	95%

Standard Procedures	
Inventory	0.10%
Strain ID	0.11%
Equip Maint	0.34%
Incident Response Plans	0.26%
PPE Program	0.19%
GLP	0.20%
Management	
Roles and responsibilities	1.65%
Commitment	0.59%
Documentation	0.26%
Drills	0.26%
Review	0.53%

Likelihood of Percutaneous Exposure

Likelihood of percutaneous exposure to individuals in the laboratory

	Weights
Type of Material	
Quality	3.78%
Quantity	1.40%
Exposure Potential	
Sharps	17.50%
Breakable	6.68%
Equipment Maintenance	7.64%
Animals	
Quality of Animals	
Number	15.75%
Size	15.75%
Multiple Species	10.40%
Bite	10.40%
Sharps and Animals	10.40%
Exposure Mitigation	
Procedures	
Gloves	16.90%
Handling	12.67%

Specific Sharp Handling Procedures	23.23%
Standard Procedures	
Inventory	0.10%
Strain ID	0.11%
Equip Maint	0.34%
Incident Response Plans	0.26%
PPE Program	0.19%
GLP	0.20%
Management	
Roles and responsibilities	1.65%
Commitment	0.59%
Documentation	0.26%
Drills	0.26%
Review	0.53%
Animals	
Handled in	6.60%
Transported in	6.60%
Handled by hand	6.60%
Specific Handling Procedures	6.60%

Likelihood of percutaneous exposure to community outside laboratory

Type of Material	
Quality	10.22%
Quantity	3.78%
Sharps in use	86.00%
Exposure Mitigation	
Waste Handling	95.00%
Standard Procedures	
Inventory	0.10%
Strain ID	0.11%
Equip Maint	0.34%
Incident Response Plans	0.26%
PPE Program	0.19%
GLP	0.20%
Management	
Roles and responsibilities	1.65%
Commitment	0.59%

Documentation	0.26%
Drills	0.26%
Review	0.53%

Likelihood of Contact Exposure

Likelihood of Contact Exposure to individuals inside the laboratory

	Weights
Type of Material	
Quality	6.85%
Quantity	2.53%
Cont Exposure	
Spill	23.62%
Waste	11.52%
Surfaces	14.98%
Decon	7.49%
Animals	
Quality of Animals	
Number	8.25%
Size	8.25%
Multiple Species	5.45%
Ability to Shed	5.45%
Animal Waste	5.45%
Exposure Mitigation	
PPE	
Gloves	8.98%
Clothing	5.05%
Eyewear	5.05%
Shoes	2.24%
Procedures	
Absorbent mat	5.61%
Handing Processes	8.42%
Spill Clean up	7.29%
Skin protection	13.46%
Standard Procedures	
Inventory	0.10%
Strain ID	0.11%
Equip Maint	0.34%

Incident Response Plans	0.26%
PPE Program	0.19%
GLP	0.20%
Management	
Roles and responsibilities	1.65%
Commitment	0.59%
Documentation	0.26%
Drills	0.26%
Review	0.53%
Animals	
Handled in	7.01%
Transported in	7.01%
Animal Handling	7.01%
Animal Waste Handling	7.01%

Likelihood of Contact exposure to the community outside the laboratory

	Weights
Likelihood of Exposure	
Type of Material	
Quality	10.22%
Quantity	3.78%
Procedures	
Waste	86.00%
Exposure Mitigation	
Standard Procedures	
Inventory	2.16%
Strain ID	2.43%
Equip Maint	7.56%
Incident Response Plans	5.94%
PPE Program	4.32%
GLP	4.59%
Management	
Roles and responsibilities	36.50%
Commitment	13.14%
Documentation	5.84%
Drills	5.84%
Review	11.68%

Likelihood of Ingestion

Likelihood of exposure through ingestion to individuals in the laboratory

Type of Material	
Quality	10.22%
Quantity	3.78%
Ingestion	
Exposure	
Spill	35.26%
Decon	11.18%
Exposure	
Mitigation	
PPE	
Gloves	9.50%
Face Shields	5.35%
Procedures	
Handling Procedures	8.91%
Hands washed	7.72%
Standard	
Procedures	
Inventory	0.10%
Strain ID	0.11%
Equip Maint	0.34%
Incident Response Plans	0.26%
PPE Program	0.19%
GLP	0.20%
Management	
Roles and responsibilities	1.65%
Commitment	0.59%
Documentation	0.26%
Drills	0.26%
Review	0.53%

Likelihood of exposure through ingestion to the community outside the laboratory

	Weights
Type of Material	
Quality	10.22%
Quantity	3.78%
Procedures	
Solid Waste Handling	62.78%
Liquid Waste Handling	23.22%

Exposure Mitigation		
Standard Procedures		
	Inventory	2.16%
	Strain ID	2.43%
	Equip Maint	7.56%
	Incident Response Plans	5.94%
	PPE Program	4.32%
	GLP	4.59%
Management		
	Roles and responsibilities	36.50%
	Commitment	13.14%
	Documentation	5.84%
	Drills	5.84%
	Review	11.68%

Consequences of Disease

Consequences of Disease to Humans

Agent Characteristics		
	Mutagenic	3%
	Enzyme	3%
	Immune suppress	3%
	recombine	2%
Morbidity		
	Duration of ill	4%
	Severity of ill	15%
	Duration of infec	3%
	Sequeal	4%
Mortality		62%
Mitigation		
	Diagnosis	14%
	Treatment	30%
	Vaccine	36%

Consequence of Disease to Animals

Morbidity		31%
Species		69%
Mitigation		
	Diagnosis	14%
	Treatment	30%
	Vaccine	36%

Secondary Consequences to Humans

Routes		
	Inhalation	6%
	Perc	2%
	Contact	3%
	Ingestion	2%
	Vector	2%
	Vertical	1%
	Sexual	1%
Transmission		
	human to human	21%
	animal to human	11%
	human to animal	5%
Stability		20%
Reportability		25%

Secondary Consequences to Animals

Routes		
	Inhalation	6%
	Perc	2%
	Contact	3%
	Ingestion	2%
	Vector	2%
	Vertical	1%
	Sexual	1%
Transmission		
	Animal to human	19%
	human to animal	9%
	animal to animal	9%
Stability		20%
Reportability		25%

Appendix B – Excerpts from external validation reports

The laboratories that participated in the validation of this model come from countries which include: Botswana, Ethiopia, Gabon, Kenya, Tanzania, Uganda, Canada, Egypt, Argentina, New Zealand, US, Belgium, Pakistan, United Kingdom, India, Switzerland, Bolivia, Brazil, Cuba, Ecuador, Panama, Mexico, and, Trinidad & Tobago. The laboratories which provided detailed risk assessment results include: Egypt, India, Switzerland, Germany, the UK, Pakistan, Uganda, and the US.

A questionnaire was provided to all reviewers as well as the pilot version of the model (this pilot version of the model was created using Microsoft Excel©). The model included all the questions, weights, and mathematical calculations and provided the user with a graphical view of the relative risks.

The questionnaire and some experts from users:

1. Did the results as presented from the tool match your expert judgment of the level of risk(s)? If not, please explain how the results varied from your expiations?

Yes – although my assessment of the agent would normally be only on the class … But yes the overall risk ratings would be similar

The results generated by the tool did match my judgment of the risk level.

Yes, they did match.

2. Did the results being broken into the different characterizations (multiple points on the graph) help in better understanding the risks and help in determining possible risk mitigation approaches?

Yes – very well done

Yes the break down of the results helped. However, a more detailed explanation/definition of all the risk categories would help.

Yes, the approach is right

I like the principle idea. However, I wonder whether it would not be clearer if, at least for the community, the risks were summarised. As far as the individuals are concerned, I believe this is a good approach.

3. Did the questions make sense, were there any that were confusing? For any question, was there not an appropriate pre-defined answer as an option?

Questions were very clear & options were well covered.

Largely they are good, but still in some places they may need modification.

4. Will you continue to use a tool or model like this for other assessments?

Yes

Yes; we are basing our risk assessments on your model and hope to complete 40 over the next few months.

I would definitely like to do that. I generally like the approach taken. It comes across as a very thorough model taking in a lot of different angles.

Yes, very much. I would use this approach first then would go manually in detailed.

5. Are there any specific changes, features, or issues with the model or tool you would like to see in the final release?

I think it may be possible to shorten the section on laboratory procedures & remain an effective assessment on the set up of the facility

Add an additional column behind the scores for remarks
I'd like to see the scales on both graphs (human and animal)

It would be great if a summary report could automatically generate that summarizes the title page and the graph so it can be printed out and accompany an SOP.

Over 20 unique agent biosafety assessments were returned, 45 separate laboratory procedures.

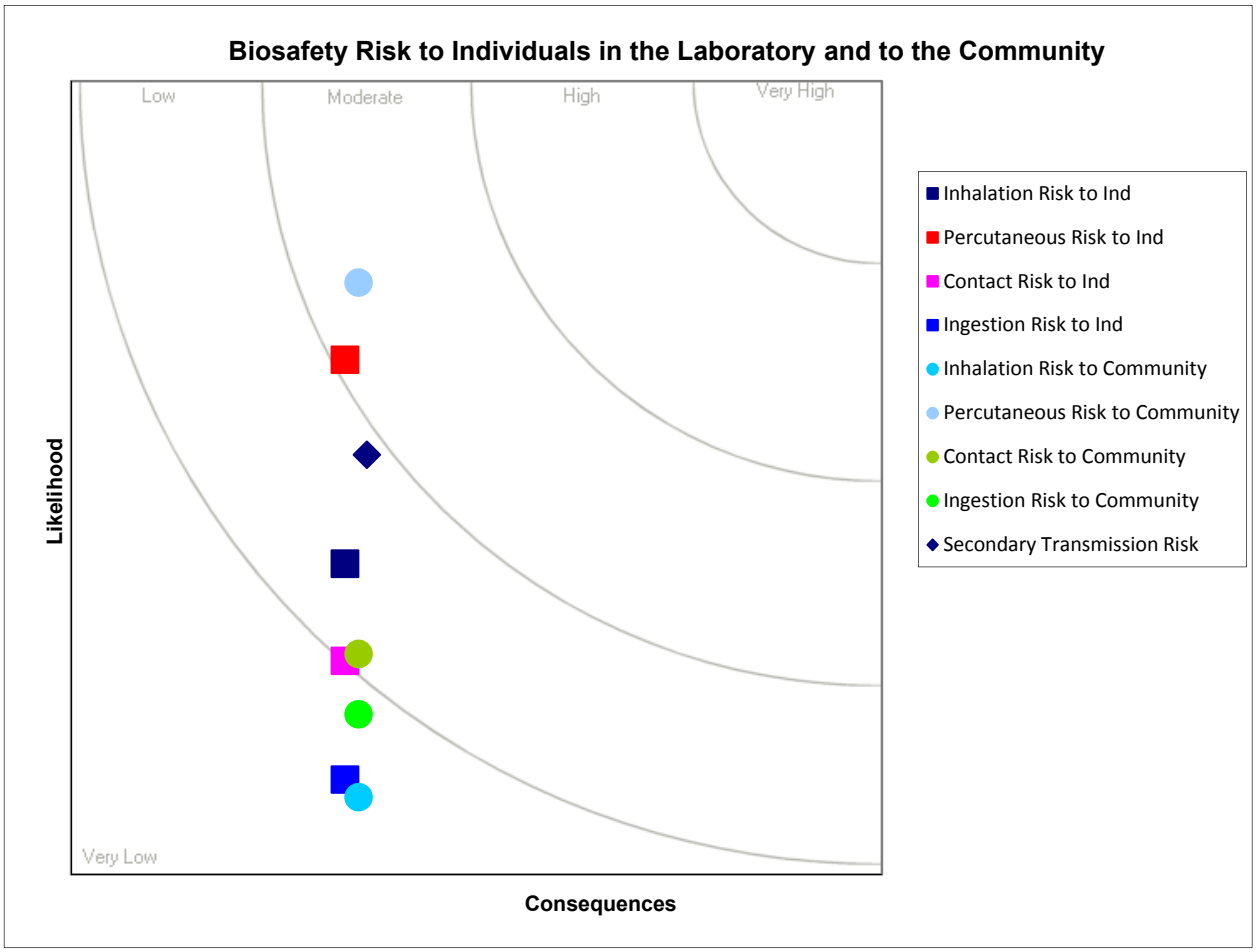

Figure 11: External review results from laboratory working on KFDV

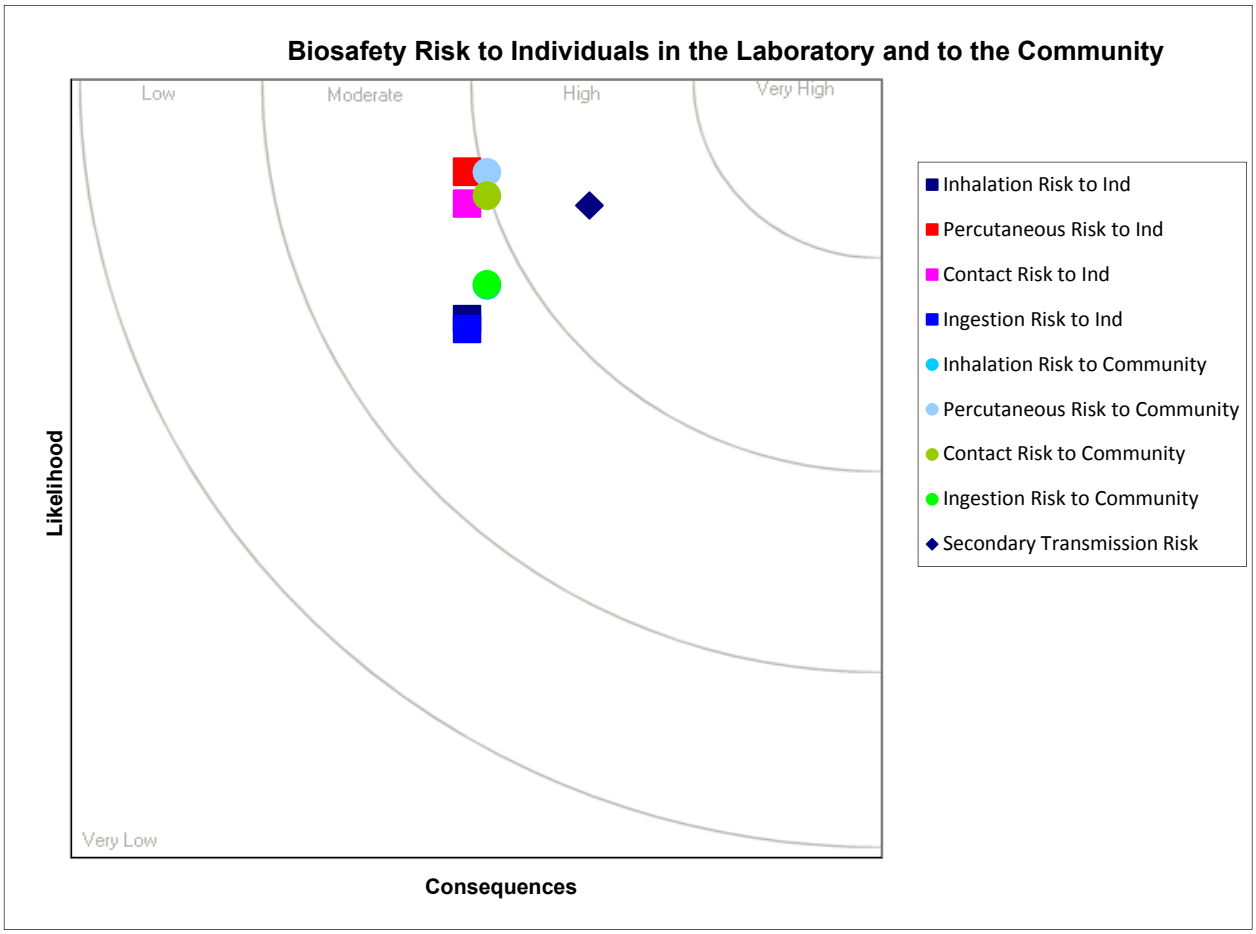

Figure 12: External reviewer results from a laboratory working on SARS prior to mitigation

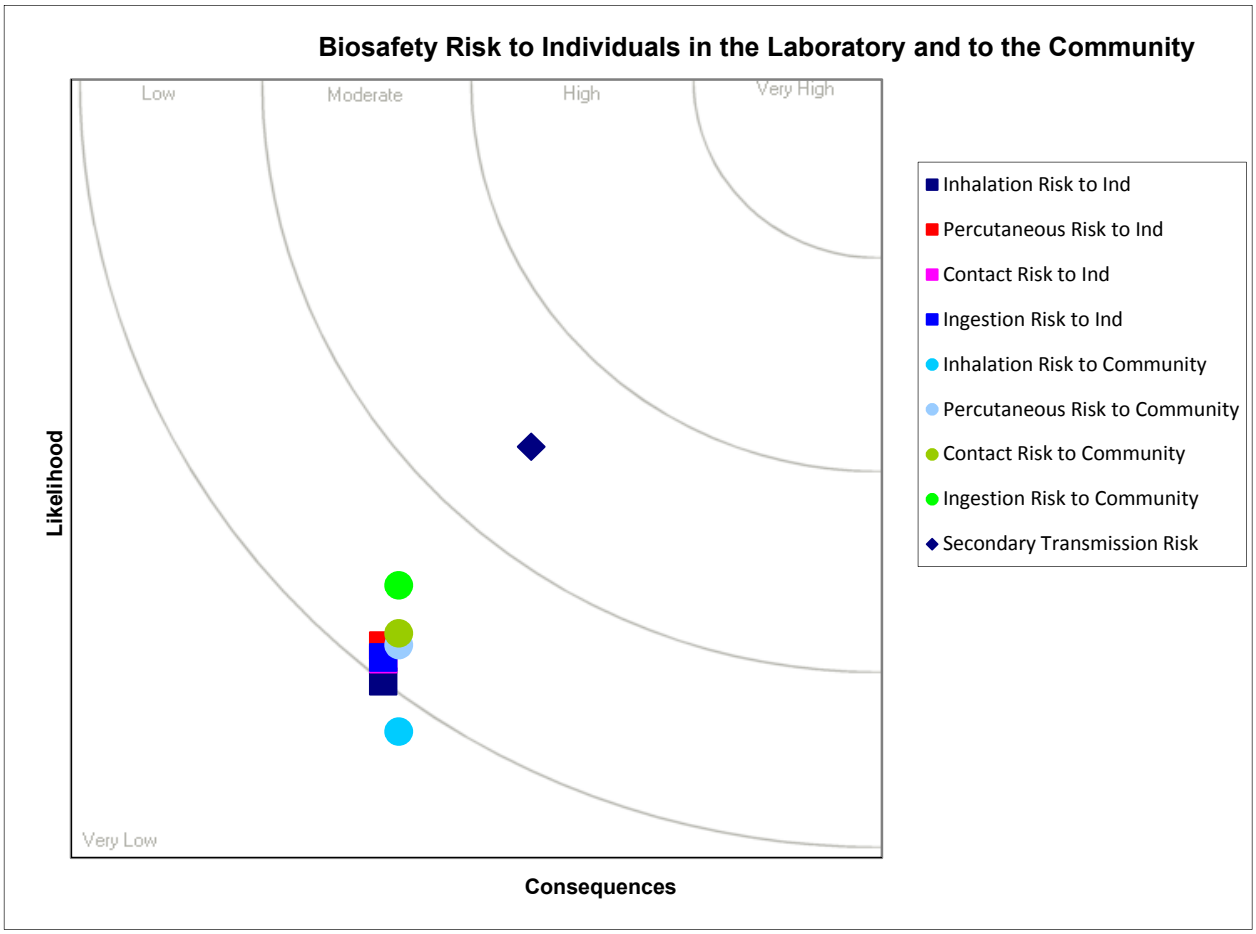

Figure 13: External reviewer results from a laboratory work on SARS after implementing mitigation

Some specific quotes from external reviewers:
"My score: model is almost 95% perfect." Reviewer from high containment laboratory in India
"In general, I found the model quick and easy to use." Reviewer from a private biotech firm

Appendix C – Results from NIH risk group and model review

As part of the validation activities of this project, 17 biological agent risks were modeled using the Biosafety RAM. The laboratory activities were normalized for all the agents and the worst-case likelihood and consequences used. NIH has defined multiple biological agents as risk group 1 to 4 depending on specific agent characteristics. This review was to compare how agents when ranked using the Biosafety RAM model compared to the NIH risk group list. The two risk group 4 agents modeled included Ebola Zaire and Marburg virus; the risk group 3 agents included: *Burkholderia pseudomallei*, *Yesinia pestis*, Monkeypox virus, *Mycobacterium tuberculosis*, Avian influenza H5N1 virus, Rift Valley Fever virus, Human immunodeficiency virus, Yellow fever virus, SARS Coronavirus nor *Brucella meltinsis* have been defined by the

NIH but are typically treated as risk group 3; *Pseudomonas aeruginosa, Shigella,* Rabies virus, and Hepatitis B virus are categorized by NIH as risk group 2; *E.coli* K-12 is risk group 1.

Several studies using these agents and their resulting scores in Biosafety RAM produced some interesting results. When comparing only the likelihood of infection/exposure of these agents, when taking the worst case likelihood, the agents cluster around the possible routes of infection: with known inhalation potential ranking highest, followed by possible inhalation potential, and finally those agents which have no possible potential for infection from inhalation. *E. coli* K-12, which has a very low likelihood of infection due to the modified nature of the strain, ranked significantly lower.

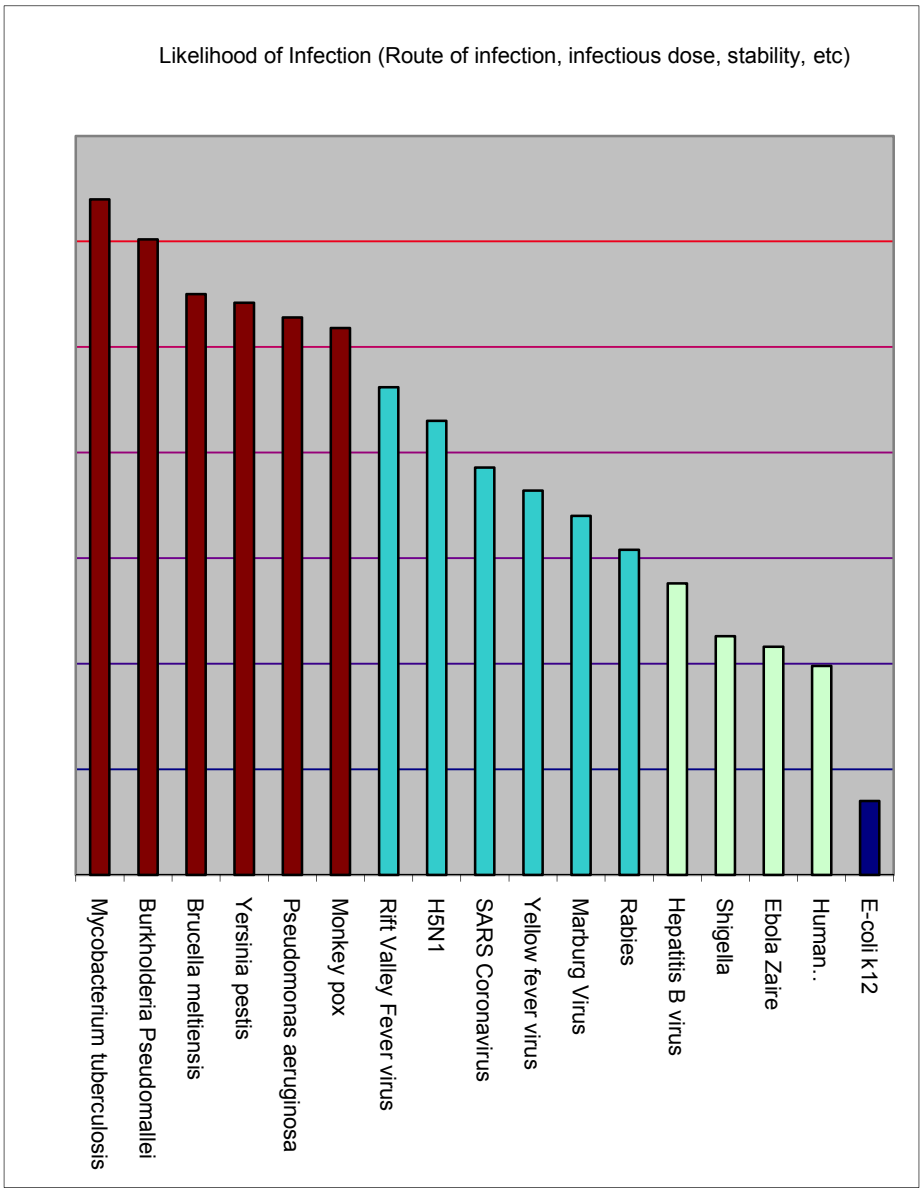

Figure 14: Likelihood of infection ranking

These agents were also ranked by the consequences of disease to a human host assuming infection. Both the mitigated and unmitigated consequences were calculated. These results highlighted the dramatic impact of consequence mitigation. The ranking of the agents, when looking at the mitigated consequences is very similar to the NIH risk group definitions.

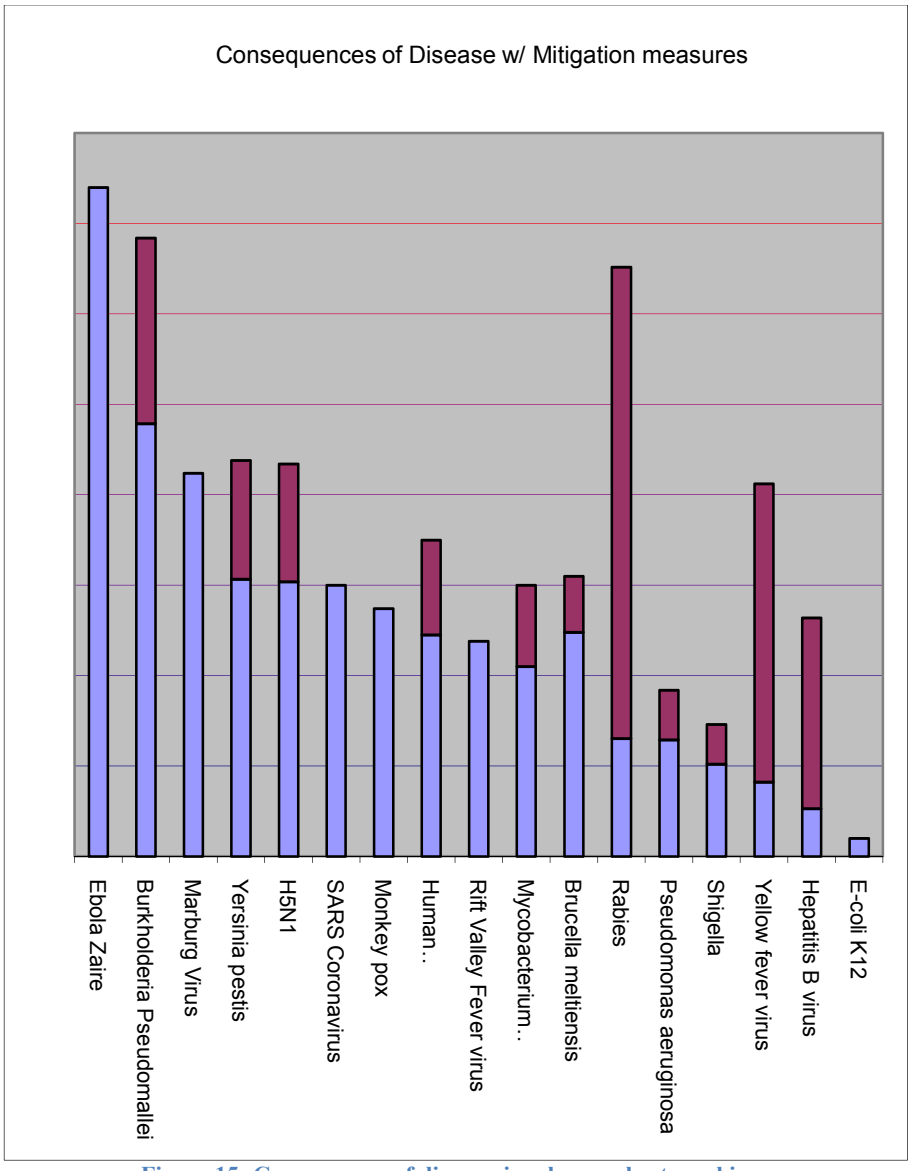

Figure 15: Consequence of disease, in a human host, rankings

These results can be combined to look at the biosafety risk of these agents. Those results can be viewed in Figure 8. The final calculated scores for likelihood and mitigated consequences are below.

Agent Name	Likelihood	Mitigated Consequences
Ebola Zaire virus (RG4)	1.08	3.7
Burkholderia pseudomallei (RG3)	3.01	2.39
Marburg virus (RG4)	1.7	2.42
Yersinia pestis (RG3)	2.71	1.53
Monkeypox virus (RG3)	2.59	1.37
Mycobacterium tuberculosis (RG3)	3.2	1.05
Avian influenza H5N1 virus (RG3)	2.15	1.52
SARS Coronavirus (No NIH guidance, but treated as RG3)	1.93	1.5
Rift Valley Fever virus (RG3)	2.31	1.19
Brucella meltiensis (No NIH guidance, but treated as RG3)	2.75	0.8
Pseudomonas aeruginosa (RG2)	2.64	0.64
Human immunodeficiency virus (RG3)	0.99	1.23
Rabies virus (RG2)	1.54	0.652
Yellow fever virus (RG3)	1.82	0.412
Shigella (RG2)	1.13	0.511
Hepatitis B virus (RG2)	1.38	0.264
E-coli k12 (RG1)	0.35	0.08