Sandia National Laboratories

BioRAM Security User Guide

Global Chemical and Biological Security Program

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National Nuclear Security Administration

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1. INTRODUCTION

Sandia National Laboratories' Global Chemical and Biological Security program (SNL/GCBS) has an on-going mission to enhance laboratory biosafety and biosecurity. SNL/GCBS has developed robust biosafety and biosecurity risk assessment methodologies and tools to aid laboratories seeking to implement biosecurity as advocated in the recently released World Health Organization's "Biorisk Management: Laboratory Biosecurity Guidance." BioRAM Security (BioRAM) is one of these tools. This tool was designed to complement the "Laboratory Biosecurity Handbook" written by Ren Salerno and Jennifer Gaudioso (Salerno, 2007). BioRAM was originally developed under the Sandia National Laboratories Laboratory Directed Research and Development (LDRD) process and has been updated with support from the US Department of Health Centers for Disease Control Select Agent Program, the US Department of State Biosecurity Engagement Program, and by funding from Sandia National Laboratories' Associated Laboratories Directors.

The main objective of BioRAM is to strengthen risk governance in the laboratories by providing assessment methods that are standardized, systematic, and repeatable. The tool's results show the relative risk of biological materials at the given facility (or specific laboratory) and give program management a mechanism to determine risks that are unacceptable. This tool can aid management in allocating resources to mitigate facility biosecurity risks; and to assess current biosecurity risk program management effectiveness.

The BioRAM tool was initially designed for biorisk officers to assist them in the identification, the understanding, and the communication of biorisks present in a laboratory and how to mitigate those risks. The tool was developed leveraging integrating knowledge from Sandia National Laboratories' security subject matter experts (SMEs) and international biorisk officer experiences focusing on a performance-based assessment of risk. That is, the collected measures were assessed on what they do rather than how they accomplish the task. For example, when the tool asks about a perimeter barrier it does not specifically ask about the type of fence (i.e., if this is a chain link fence) but rather does the barrier effectively complete the perimeter. This tool supports the assessment of laboratories from around the world where resources for security are variable and novel solutions maybe required. The expert team developed the weighted criteria and outlined the underlying scoring functions for the criteria focusing on their experiences, expertise, and considering the overarching principles of security.

As this tool was designed to complement the "Laboratory Biosecurity Handbook" (Salerno, 2007), the tool characterizes a biological facility or laboratories biosecurity system effectiveness based on the five pillars of biosecurity: physical security, personal reliability, transport security, information security, and the overall security management of the facility. This is complemented by the evaluation of the risks of misuse of biological materials existing at the facility - likelihood of someone targeting biological materials at a facility for theft and the consequences of malicious use of the biological materials - creating a final relative biorisk value.

1.1. Methodology Overview

The underlying methodology within the BioRAM tool is based on structured risk assessment methodologies used across the U.S. government's critical infrastructure (Biringer, 2007). Garcia (Garcia, 2008) defines security risks based on the intentionality of the threat actor, the ability of the

threat actor to achieve their intended goal, and the consequences of achieving this goal—simplified mathematically as:

$$Risk = P_A \times (1 - P_E) \times C$$

P_A = probability of attack (for a specified timeframe) – this reflects the intentionality of the threat actor
P_E = probability that the facility's security system will be effective against an attack – this reflects the security system's effectiveness at changing or reducing the ability of the threat actor to achieve their goal
C = Consequence of attack – the consequences of the threat actor achieving their goal.

In BioRAM, the probability of an attack, P_A, has been reflected to focus on the relative attractiveness of the biological facility as a theft target, based on having desired biological materials that are useful in the development of a biological weapon. The probability the security system will be effective against an attack, P_E, is based on the level of implementation of security measures to include physical security, transport security, cyber security, insider protection, and overall risk management of the laboratory. This value is inverted to reflect gaps in security. The consequences of attack, C, are defined in BioRAM as the human and/or animal health impacts following the use of the material as a biological weapon. The BioRAM tool reflects the overall risk as a two-dimensional function where P_A x (1-P_E), the theft potential, is illustrated on the Y-axis and C, reflecting the consequences of the attack, is illustrated on the X-axis.

The model that support the tool consists of a series of questions; whose answers are reflected as a value. The tool provides discrete numbers reflecting the answer options; however, the user of the tool can answer any question with a continuous value between 0 and 1, but they should use the defined discrete values to help guide their final number. This value is then combined with the tool defined weight, these weighted values are then combined (as a weighted average) to create the overall scores defining P_A, P_E, and C.

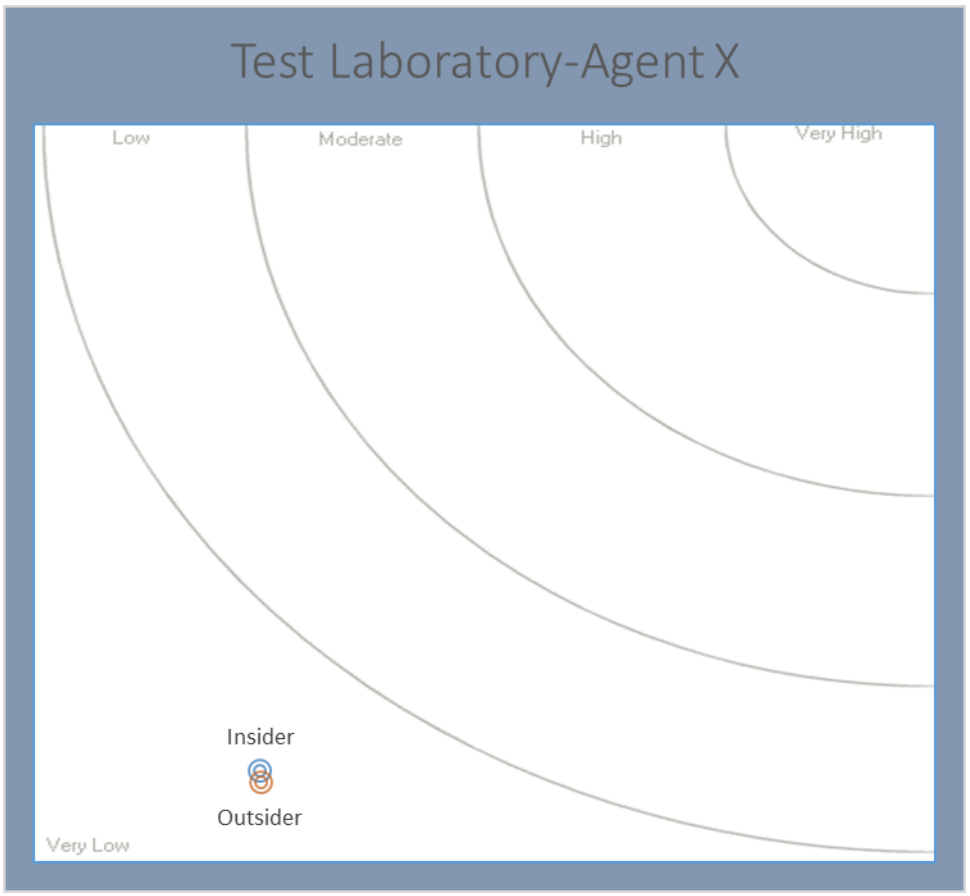


Figure 1: Two-dimensional reflection of the probability of attack combined with the effectiveness of the security system against the attack (theft potential) (Y-axis) and the consequence of the attack (X-axis)

As mentioned, BioRAM is based on a well-developed security risk assessment methodology. The formal qualitative modeling within BioRAM is based on a multiple-objective decision model. Multi-objective models (Keeney, 1976) have been shown to be effective in many application areas. Caskey et al. (Caskey, 2013) developed a series of multi-objective models to assess the threat posed by non-state actors within countries of interest to acquire or develop nuclear, chemical, and biological weapons in combination with the presence and vulnerability of agents in the country. Ezell et al. (Ezell, 2000) (Ezell B. , 2007) developed multi-objective models that quantified vulnerability as a measure of susceptibility to a range of threat scenarios. Ewing et al. (Ewing, 2005) utilized a similar model considering the tradeoffs regarding U.S. military base closures resulting is a massive savings of U.S. dollars.

While the results of the tool are quantitative, this model is not intended to provide an assessment of absolute risk but rather provide a structured method for the comparison of the relative risks posed by laboratory practices and by biological material present at a facility.

1.2. Tool Overview

The BioRAM software tool was developed as open source software per the requirements from the tool's funding agencies. The tool, provided directly from Sandia National Laboratories or downloaded from the software repository (https://github.com/sandialabs/BioRAM) contains the values and assumptions provided in this manual. Any versions that have been modified by users may not reflect the same results. This overview also reflects only the security elements of BioRAM and not those included in the safety version. BioRAM falls under copyright 1186.1 Biosecurity Risk Assessment Methodology (BioRAM) v. 4.0, 2019.

The software exists in three distributed formats, raw Excel files, a Window's .Net platform, and a Java platform, a future version will be released in a direct executable format that incorporates both safety and security into a single risk assessment tool. Currently, the Excel and the Java versions are distributed – the .Net version is available upon request.

1.3. Verification and Validation

The BioRAM tool has undergone a series of verification and validation activities. The first of these is the verification of the relevance of the questions, the underlying value function, and the weights.

BioRAM was developed as a consensus performance-based model relying on expert judgements regarding biosecurity. The initial defined equations were leveraged heavily from those having already been verified and applied in the real world (Biringer, 2007) (Garcia, 2008). As such the highest-level equations were not subject to further verification. The underlying sub-topics and subsequence questions were externally peer reviewed by those with unique domain knowledge. Those included experts from within Sandia National Laboratories, but external to the project, as well outside agencies. Outside agencies include the U.S. Centers of Disease Control Select Agent Program, the Public Health Agency Canada, and the National Institutes of Health Japan. These experts also reviewed the underlying value model and weights associated with each of the questions.

Additionally, the weights, value functions, and equations were validated using synthetic data. This data was specifically designed to reflect actual laboratory situations and seeded to highlight potential elements of the biological materials or the security system's effectiveness.

The final BioRAM security validation was based on direct user feedback and questions, specifically those users under the regulatory control of the U.S. Select Agent Program.

2. DETAILED METHODOLOGY

The main objective of BioRAM is to strengthen risk governance in the laboratories by providing assessment methods that are standardized, systematic, and repeatable. The tool's results show the relative risk of biological materials at the given facility (or specific laboratory) and give program management a mechanism to determine risks that are unacceptable. This tool can aid management in allocating recourses to mitigate facility biosecurity risks; and to assess current biosecurity risk program management effectiveness.

The BioRAM model is a risk assessment model; as such, it calculates both likelihood and the consequences and uses both to support the relative comparison between laboratories, materials, and processes. The BioRAM tool includes criteria (questions) which evaluate the relative attractiveness of the biological facility as a theft target, the level of implementation of security measures, and the human or animal health impact if the misuse of a biological materials acquired from the facility is successful. Based on these definitions, the properties of a biological material influence how attractive it is for malicious use (which directly influences a laboratory's level of attractiveness) and influences the consequences of malicious use. The laboratory's existing security posture and implemented measures influence the facility's susceptibility to theft; these are measured by considering someone without authorized access to the laboratory housing the biological materials as well as someone with authorized access. The tool provides discrete numbers reflecting the answer options; however, the user of the tool can answer any question with a continuous value between 0 and 1, but they should use the defined discrete values to help guide their final number.

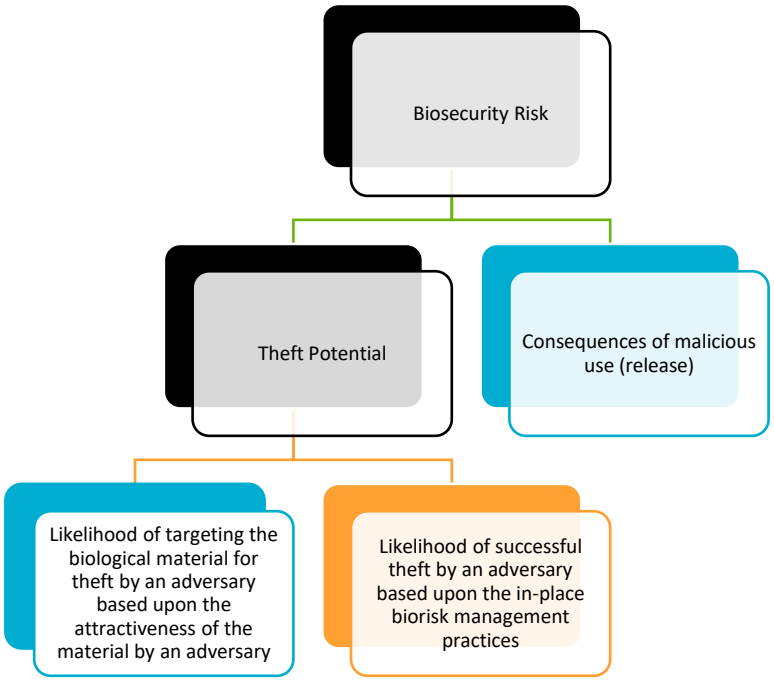


Figure 2: Biorisk Assessment Methodology

The BioRAM tool is organized into two top-level topics, each with a series of subtopics and then, finally, the specific risk assessment questions. This portion of the guide will dive into each topic,

sub-topic and the questions asked to outline the how each impacts the final risk (either negatively or positively) and the implications.

The topics include:

- Agent (the properties of the biological material) – boxes colored blue in Figure 2
- Facility (the level of implementation of security system measures) – boxes colored orange in Figure 2

The details presented in this section are based on those from a 2017 update of the model. As such, depending upon the software tool used, not all these questions may be relevant. The 2017 model update included discussion and review from Sandia National Laboratories' biosecurity experts and biorisk experts from across the globe.

2.1. Agent (properties of the biological material)

This topic has questions designed to help characterize biological materials (agents) existing within the laboratory. Questions focus on factors that influence the attractiveness of the biological material to an adversary who has the goal of using the acquired material as a biological weapon, as well as the factors that influence the consequences of successful misuse (toward humans or toward animals). These are reflected in Figure 2 in the blue colored boxes. The top-level sub-topics for biological materials (agents) are:

- Attractiveness of the biological material as a potential biological weapon (attractiveness); and,
- Consequences of successful misuse against a human population and/or against an animal population (focusing on animals who are part of the food chain) (consequences).

The properties of the biological material are defined by a series of questions; whose answers are defined by a value. The tool provides discrete numbers reflecting the answer options; however, the user of the tool can answer any question with a continuous value between 0 and 1, but they should use the defined discrete values to help guide their final number. This value is then combined with the tool defined weight, these weighted values are then combined (as a weighted average) to create the overall scores defining P_A or C. For some questions, the discrete value ranges from 0.1 to 1 rather than 0 to 1, this reflects the SME defined 'lowest' value for the question. Where the discrete values appear to jump – that is go from .1 to .25 to 1 – this reflects an SME defined non-linear value function.

2.1.1. Attractiveness

Recall that in BioRAM, P_A has been defined as the relative attractiveness of the biological facility as a theft target. Attractiveness is defined based on three subtopics:

- Utility of the material for misuse,
- Production requirements of the material; and,
- Dissemination options.

Each of these three subtopics has been given a weight by subject matter experts in biorisk management and threat actor behaviors that reflects its contribution to defining the overall attractiveness of the biological material for misuse. The figure below reflects the defined weights.

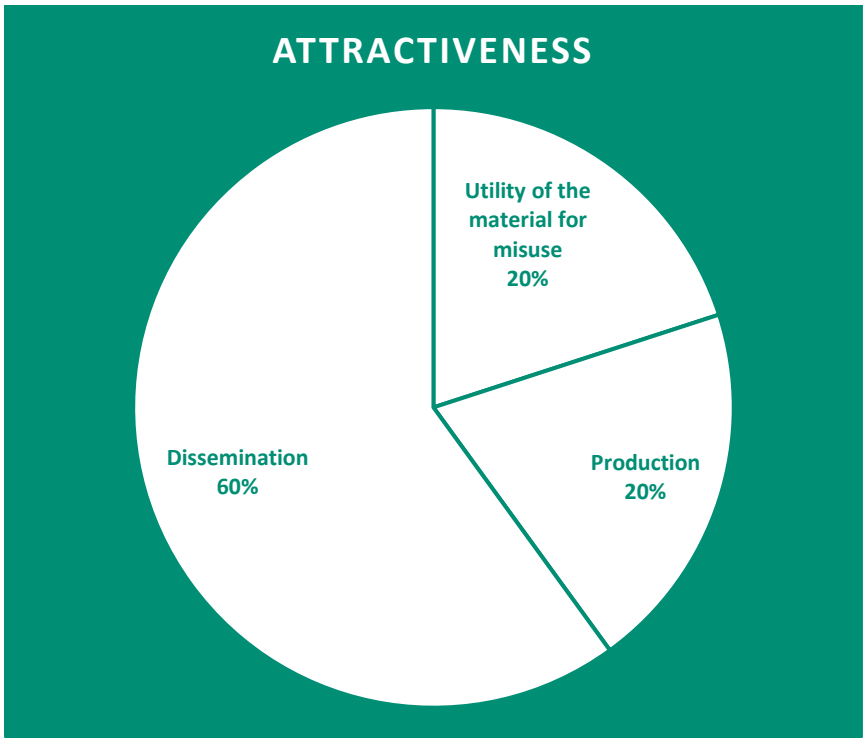


Figure 3: Weights defined by SMEs reflecting the contribution of the three subfactors defining attractiveness of a biological material to someone with malicious intent

For each question used to define the subtopics, the subject matter experts defined a question specific weight and ordinal values reflecting the various answer options. As such, the equation to define the P_A for any biological material is based on a weighted average of the answer values for each question and its associated weight.

$$P_A = \sum_{i=0}^{n} Ai, wi$$

Where A is the value defined for each of the questions (*i*) under the attractiveness category and *w* is the defined weight for the question.

The following sections detail the specific questions under each of the three subtopics.

2.1.1.1. Utility of the material

The utility of the material for malicious purposes is based on three questions, one based upon the procedures within the laboratory and two based on the biological agent itself.

The full laboratory procedure question set is needed to assess both security and safety risks within a laboratory, however for the evaluation of the biosecurity risk, the only security relevant question focuses on the procedures or work conducted within the laboratory:

L1. What type of material will be used in this procedure?	Environmental Samples (soil, water, etc.) = .1	Diagnostic Samples (blood, urine, tissues samples, saliva, etc.) = .25	Purified biological materials (stock culture) = 1

This answer choices to this question (L1.) involve a range from environmental samples, to diagnostic samples, to purified biological materials (aka isolates). The purpose of this question is to determine the value of the biological material to someone with malicious intent. Subject matter experts have determined an isolate is far more useful in developing a biological type weapon than a diagnostic or environmental sample.

The two questions focusing on the biological agent itself are:

1. What is general population's knowledge or awareness of this agent as related to biological weapons or bio-crime?	No history of this agent in biowarfare, bio-crime or bioterrorism and no evidence of terrorist interest in this agent = .1	Agent has no history of use, but there is evidence of interest by criminals or terror groups = .75	Agent has a history of use in bioterrorism, bio-crime, or biowarfare = 1
2. What will the level of social impact (public panic, rioting, people being unwilling to go out and work, fear of additional incidents) of the disease caused by this agent occurring in the country?	The social impact of an agent release from the facility would be negligible = .05	The social impact of an agent release from the facility would be moderate =.5	The social impact of an agent release from the facility would be catastrophic =1

The first of these two questions (1.) may be answered in one of several answer choices: : - no history of use of the agent in biowarfare, bio-crime or bioterrorism and no evidence of terrorist interest in this agent" - to – "the agent having a history of use in bioterrorism, bio crime, or as a biological weapon". The objective of this question is to determine if the biological agent would be considered valuable for malicious use by the public. The subject matter experts acknowledged that history of use does not equate to future use, but based on behaviors of adversaries, the experts believed history has some relevance in measuring the biological agent's attractiveness.

The answer choices for the second of these questions (2.) range from a negligible social impact to a catastrophic impact. While this question seems to have more relevance in understanding the consequences of misuse, the subject matter experts determined that the potential impact was also relevant in understanding the interest in a biological material by those with malicious intent.

2.1.1.2. Production of the agent

This section provides an understanding of the relative ability of someone to produce this biological material in sufficient quantity and state to be used as a biological weapon. This section is comprised of three questions:

3. What is the level of microbiological skill required to grow a suitable quantity (to meet the malicious objective) of this agent?	Groundbreaking techniques would be required to grow a suitable quantity of this agent = .05	Production of a suitable quantity of this agent requires advanced technical skills = .25	Production of a suitable quantity of this agent is straightforward for an individual with undergraduate level microbiological skills = .75	Suitable quantity of this agent could be produced easily with limited microbiological skills = 1
4. What is the general accessibility of production equipment required to produce this agent?	Production equipment is difficult to acquire and legal restrictions exist regarding procurement = .1		Production equipment is difficult to acquire due to cost =.5	Production equipment can be easily acquired or fabricated = 1
5. What are the storage requirements for this agent?	Agent is not stable = .05	Agent is stable for days - weeks =.5	Agent is stable long term, but cold storage required =.75	Agent is stable long-term without cold storage =1

In terms of the first question (3.), answers choices span from "Production not required for misuse" to "Production virtually infeasible". This question highlights the importance of the technical skill of the threat, as production is based upon the skills for production and storage. An unskilled entity who wishes to use a biological material as a biological weapon will be less of a threat than a threat with extensive microbiological skills.

The second question (4.) focuses on the equipment necessary to produce an agent. Some production equipment is very difficult to attain and may have legal restrictions existing limiting procurement. On the other hand, other production equipment is easily attainable, or can be easily made by the adversaries.

The final question (5.) is designed to ascertain how the storage requirements for an agent will affect the production of the agent. As differing biological material can survive in various types of environments, it is important to consider the stability of an agent and the potential of its survival outside of a laboratory setting. For this question, unstable biological material is given a very low score, whereas biological material that can survive without cold storage is given a high score.

2.1.1.3. Dissemination

In the BioRAM tool, dissemination is based on the possible routes of infection, the dose for that route, the environmental stability of the biological material, and the feasibility of host to host transmission. The rationale is based on the idea that biological material is more attractive to an adversary to use as a BW if dissemination is less complex, e.g. simple aerosol with a low infectious

dose that is stable is more attractive than, for example, a biological material that can only cause disease if directly injected into the blood stream.

There are seven BioRAM questions in this section, most of which have their own corresponding sub-sections. Each question's responses range from "Dissemination feasible", the highest scoring option, to "Dissemination virtually infeasible", the lowest scoring option. The first five questions each have their own sub-question which aims to ascertain the infectious dose (ID50) of the agent – if the ID50 is less than 1000, the user marks the "Yes" option.

The first few questions in this section are as follows:

6. 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)?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1
6a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	No = 0			Yes = 1
7. Is this agent known to cause infection via percutaneous exposure (to cause infection through compromised skin or direct injection into the blood stream)?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1
7a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	No = 0			Yes = 1
8. Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes)?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1
8a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	No = 0			Yes = 1
9. Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract)?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1
9a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	No = 0			Yes = 1
10. 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))?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1
10a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	No = 0			Yes = 1

The first question's (6.) purpose is to determine the infectious route of the agent – the question focuses on if the agent causes infection via inhalation. The answers to this question will determine if

infection via inhalation is feasible. The second question (7.) focuses on percutaneous exposure and has a similar goal as the first question – to ascertain the feasibility of percutaneous infection. The next three questions (8., 9., and 10.) follow a similar format, determining if the chosen agent can cause infection via direct contact, ingestion, and/or vector transmission.

The last two questions (11., and 12.) in this section focus on the agent's stability and if it is capable of host-to-host transmission, respectively:

11. What is this agent's stability outside of a host?	Agent not stable outside of a host = 0	Agent stable only on interior surfaces for days to weeks =.25	Agent stable in the environment for days to weeks =.75	Agent stable in the environment for months =1
12. Can host-to-host transmission be used as a dissemination pathway to execute an attack?	No = 0			Yes =1

The more stable an agent is, the more likely the agent can remain stable in the environment for months, increasing the potential of successful dissemination. Similarly, the final question (12.) reflects where host-to-host transmission is feasible, and dissemination is less complex.

2.1.2. Consequences of malicious use

Recall that in BioRAM, C – Consequences - focuses on the impacts of malicious use of the biological material (e.g. a bioweapon or BW). Consequences of malicious use are based on potential direct and indirect health impacts to a human population; consequences are calculated separately for an animal population. For biological materials that have the potential to infect both humans and animals (zoonotic) both values will exist; for biological materials that only infect either humans or animals the consequences to the other will be set zero. The subtopics used to define consequences include:

- The direct health impact (morbidity and mortality) to humans and/or animals,
- The socio-economic impacts based on a possible outbreak caused by this biological material,
- The possible mitigation measures that exist within a country (or region) that could reduce the impact; and,
- The possibility for secondary transmission.

These have been weighted by experts in biorisk management and public / veterinary health.

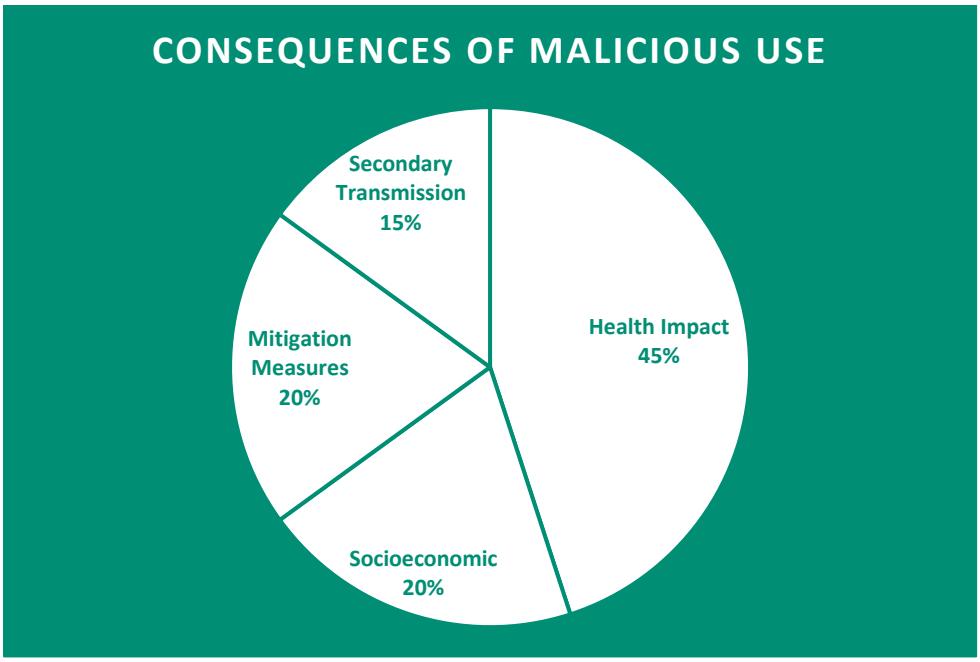


Figure 4: weights reflecting consequences of the disease caused by a release of the biological material to a human host

For each question used to define the subtopics described above, the subject matter experts defined a question's specific weight and ordinal values reflecting the various answer options. As such, the equation to define the C for any biological material is based on a weighted average of the answer values for each question and its associated weight. Separate consequence values are used to define the consequences to humans and to animals (C_H and C_A). Below are the two equations used to define consequences.

$$C_H = \sum_{i=0}^{n} Hi, wi$$

Where H is the value defined for each of the questions (*i*) under the consequence category defined for human diseases and *w* is the defined weight for the question.

$$C_A = \sum_{i=0}^{n} ANi, wi$$

Where AN is the value defined for each of the questions (*i*) under the consequence category defined for animal diseases and *w* is the defined weight for the question.

The following sections detail the specific questions under each of the four subtopics.

2.1.2.1. Health Impact

Health impacts are defined to reflect the disease morbidity in a human host, the mortality rate expected in humans, and impact to animal populations. These questions are important to consider, because the severity of which an agent can affect its host may make it more attractive to be used maliciously. A threat may see no need to disseminate an agent that has little to no effect on a population as it would result in minimal consequences. These evaluated based on health impacts for an untreated host.

Morbidity is organized considering the duration, severity, and sequela typically expected in a normal healthy adult. Each question is scored based on a value considered to have a minimal level to a significant level. The questions defining morbidity are as follows:

1. What is the duration of **illness** in a normal healthy human host?	Less than 24 hours =.1	Less than a week =.25	Multiple weeks =.5	Multiple months=.75	Signs of illness present life of host=1
2. What is the severity of illness in a normal healthy human host?	No sign of diseases=0	Low signs, host able to function but has some visual symptoms =.25	Moderate signs of disease, host able to function in a limited capacity (bed rest) =.5	High signs of disease, host not able to function (hospitalized)=.75	Extreme signs of disease, host requires mechanical assistance to sustain life, death imminent=1
3. What is the duration of **infection** in a normal healthy human host?	Less than 24 hours =.1	Less than a week =.25	Multiple weeks =.5	Multiple months=.75	Signs of illness present life of host=1
4. Does this disease cause any long-term conditions in a normal healthy human host?	No long-term impact=0	Mild long-term impacts do not impede the hosts ability to function normally=.25	Moderate long-term impact which hinders the hosts ability to function normally=.5		High long-term impact which renders the host unable to function normally=1

The first question (1.) is scored considering a short duration (less than 24 hours) to a significant duration (signs of illness present for life of host). For disease with a high mortality rate, the duration should reflect significant duration as most hosts will have signs of the disease until they die. In the second question (2.) severity is reflected ranging from no signs of disease to extreme signs reflecting mechanical assistance required to sustain life. This value should be based on the expected severity in a normal healthy adult rather than on the potential ranges of severity witnessed across the full population. Question three (3.) considers actual infection as compared to the first question focused on duration of illness. The question reflects the potential for a disease to remain subclinical within a host following infection, as this is often the case for persistent viruses. As with duration of illness,

diseases with a high mortality rate will reflect the life of the host. The final question in this section (4.) considers the potential sequela resulting from an infection. This ranges from none to a significant impact, which renders the host unable to function normally.

Mortality rates expected in human hosts is based on a single question:

5. What is the frequency of death (mortality rate) in humans caused by this disease?	No Mortality (0%) = 0	Low mortality (1% to 14%) =.25	Medium mortality (15% to 74%) =.75	High mortality (75% or more) =1

As with the serenity of illness, this question (5.) is focused on the expected mortality rate considering a generally healthy population. This rate may need to be estimated based on witnessed outbreaks as there is limited empirical data on mortality rates for many diseases. This criterion is scored based on mortality ranges defined as none, low, medium, and high with high reflecting more that 75%.

Impacts to the animal population is another factor that must be considered. Human hosts are not the only targets of malicious release of biological material, as attacking someone's livestock system may have detrimental implications on the populations that depend on them. This is the focus of the next three questions:

6. If the agent infects animals, what is the expected morbidity rate to a naïve but otherwise healthy animal population?	No Mortality (0%) = 0	Low mortality (1% to 14%) =.25	Medium mortality (15% to 74%) =.75	High mortality (75% or more) =1
7. What species of animals can this agent infect?	Affect a livestock species which has no economic impact in our country=0	Affects a less significant livestock species which is used for export and/or the by-products are a source of protein for the country=.5	Affects a single but significant livestock species which is used for export and/or the by-products are a major source of protein for the country=.75	Affects multiple, significant agricultural species which are used for export and/or the by-products are a major source of protein for the country=1
8. What is the disease impact on the general population?	Potentially affected animals are currently vaccinated for the disease caused by this agent =.1	Some potentially affected animals are vaccinated =.5		No current vaccination exists against this disease and animals at risk include young and others with compromised immune systems =1

Question six (6.) is measured like the mortality rate of humans, ranging from none to a high (75% or greater) mortality rate. This criterion may require using observed data from historical outbreaks where there is a lack of data. The next question (7.) focuses on the impact of an outbreak based on the type of animal impacted. This question does not specifically define a particular animal species, but rather reflects the species relevancy to the country (or region). This question considers a minimal value if the disease impacts species of no value to the economy of the country. A significant value reflects a disease that affects multiple, significant agricultural species which are used for export and/or its by-products are a major source of protein for the country. The final question in this section (8.) is unique to animals and reflects the impact of the disease on the actual animal population, specifically measuring the vaccine status of the impacted animals within the country (or region). This question offsets the impacts of the earlier question (6.) regarding the impact to a naïve population if the population within the country (or region) is vaccinated.

2.1.2.2. Socioeconomic impacts

The questions reflecting the socioeconomical impacts of an outbreak of the disease (caused by the biological material) are designed to reflect non-health or indirect impacts caused by BW use. The answers to these questions should be focused on the current situation of the country, region, or location that could be considered a target for the BW use. These questions consider both the direct economic impact and the indirect economic impact. External resources maybe required to support answering these questions.

9. What is the economic impact of an outbreak of this agent to the country?	The economic impact of an agent release from the facility would be negligible=.1	The economic impact of an agent release from the facility would be moderate, GDP would recover in a matter of months. =.5		The economic impact of an agent release from the facility would be catastrophic, significant impact to the GDP of the country. (Impacts of trade and tourism) =1
10. Is this agent endemic in the country?	The agent is endemic in the country=.1	The agent is not endemic in the country, but outbreaks have occurred =.75		The agent is absent in the environment of the country=1
11. Are there active eradication/control programs of this agent in the country?	There are not active control programs for this agent in this country=.1	Control policies exist but are not effective=.5	Control program is operational and is moderately effective=.75	Control program is operation and effective=1
12. Are clinical signs strong indicators of disease present? (For example, diseases that cause sudden death or diseases with obvious signs will be detected faster.)	Minimal Consequences=.1			Significant Consequences=1

The answers to question nine (9.) range from negligible to catastrophic consequences. The answer to this question also depends on the potential recovery time it would take a country to overcome the outbreak. Question ten (10.) is important because it highlights that a non-endemic agent identified in a particular country could have severe consequences to the environment of the country. If the agent already exists in the country, then the consequences should not be as severe to the environment. If the agent is endemic to the country, then eradication/control programs may already be present within the country. If the agent had been effectively eradicated, its reintroduction may have a negative outcome for the economy of the country, and this is the focus of question 11.

2.1.2.3. Impact of Disease Mitigation Measures

The next set of questions define the potential for outbreak mitigation measures to reduce the overall consequences of malicious use of the biological material.

13. Are effective diagnostic tests available in the country for humans?	Yes=.1	Yes, but difficult to use and/or only limited availability within the country=.5	No=1
14. Are effective post exposure treatments (including immuno-globulin, vaccines and anti-microbials) available in the country for humans?	Yes=.1	Yes, but difficult to use and/or only limited availability within the country=.5	No=1
15. Are preventative measures (vaccines) available in the country for humans?	Yes=.1	Yes, but difficult to use and/or only limited availability within the country=.5	No=1
16. Are effective diagnostic tests available in the country for animals?	Yes=.1	Yes, but difficult to use and/or only limited availability within the country=.5	No=1
17. Are effective post exposure treatments (including immuno-globulin, vaccines and anti-microbials) available in the country for animals?	Yes=.1	Yes, but difficult to use and/or only limited availability within the country=.5	No=1
18. Are preventative measures (vaccines) available in the country for animals?	Yes=.1	Yes, but difficult to use and/or only limited availability within the country=.5	No=1
19. Are secondary consequence measures feasible in the country for animal populations?	Isolation/quarantine/culling are feasible options in this country=.25		Isolation/quarantine/culling not feasible in this country=1

These questions highlight the country's capabilities to combat disease exposure with resources that they already possess. If diagnostic testing, post exposure treatments, and preventative measures already exist, then the consequences will be minimal, as the country already has the means to suppress the outbreak. The last group of questions (16., 17., and 18.) in this section addresses the

capacity in which biological material maliciously released can affect the **animal population.** These questions are similar to the previous set, as they ascertain the capabilities of a country to halt the spread of an unwanted biological material. The only difference with this set of questions is that they focus on the livestock population. The final question addresses a situation unique to the animal population and asks the BioRAM user to determine if isolation/quarantine/culling is a feasible option for the affected animals within the country.

2.1.2.4. Secondary transmission

This section of the BioRAM program pays close attention to the communicability of the agent, and how it could potentially continue to infect human and animal populations. This section is comprised of eleven questions that focus on the animal and human populations, as well as the potential routes of transmission for each of these groups. These questions are very similar to those defined under dissemination, but here they are linked to potential consequences.

The first four questions in this section attempt to determine if the given biological material can be spread between human hosts, via zoonotic transmission routes, and amongst animal hosts:

20. How easily does this agent transmit between human hosts?	Transmission has never been demonstrated=0	Host to host transmission suspected=.5	Host to host transmission via close contact only=.75	Agent can transmit between hosts easily=1
21. How easily does this agent transmit from animal to human hosts?	Transmission has never been demonstrated=0	Host to host transmission suspected=.5	Host to host transmission via close contact only=.75	Agent can transmit between hosts easily=1
22. How easily does this agent transmit from human to animal hosts?	Transmission has never been demonstrated=0	Host to host transmission suspected=.5	Host to host transmission via close contact only=.75	Agent can transmit between hosts easily=1
23. How easily does this agent transmit between animal hosts?	Transmission has never been demonstrated=0	Host to host transmission suspected=.5	Host to host transmission via close contact only=.75	Agent can transmit between hosts easily=1

If the disease can spread with ease amongst any of the groups mentioned in the above questions, the consequences become much more significant. If the disease is new or is not well researched, then the BioRAM user may wish to indicate that host-to-host transmission is suspected.

Transmission routes are again taken into consideration with the next batch of questions:

24. 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?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1

25. 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?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1
26. Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes) in the natural environment?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1
27. Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract) in the natural environment?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1
28. 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))?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1
29. 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)?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1
30. Is this agent known to cause infection via sexual transmission (to cause infection through sexual contact including intercourse)?	Not an infectious route = 0	Unknown =.25	A possible route of infection = .75	Infectious Route =1

As mentioned previously, some of these questions are repeated from the dissemination section. However, in this section, the focus is the potential for secondary transmission of the disease following initial misuse. These factors are important to consider, as the more routes of transmission a biological material has, the more likely significant consequences will occur. Yet, this section considers vertical and sexual transmission, increasing the scope of consequence that may occur.

2.2. Security System Effectiveness

Security systems effectiveness (P_E), as defined previously, is based on the level of implementation of security measures as outlined in the "Laboratory Biosecurity Handbook" These include the overall security culture of the facility (or laboratory), physical security, personnel reliability, transport security, material control and accountability, and information security. BioRAM does not measure specific performance of individual security system components (e.g. the ratio of false/positive alarms), but rather the level of implementation of the various security systems components. This is because BioRAM is a performance-based assessment and designed to support more general decision-making regarding security than a model designed to simulate security situations and measures based on path analysis.

The level of implementation of a security system reduces the potential for successful theft of biological materials (or other assets). The measures considered include those designed to reduce the potential for theft from both those with authorized access (insiders) and those without (outsiders).

A security system should be designed based upon the principles of layered protection. Below are the weights defined by security systems experts reflecting protection against an outsider and an insider.

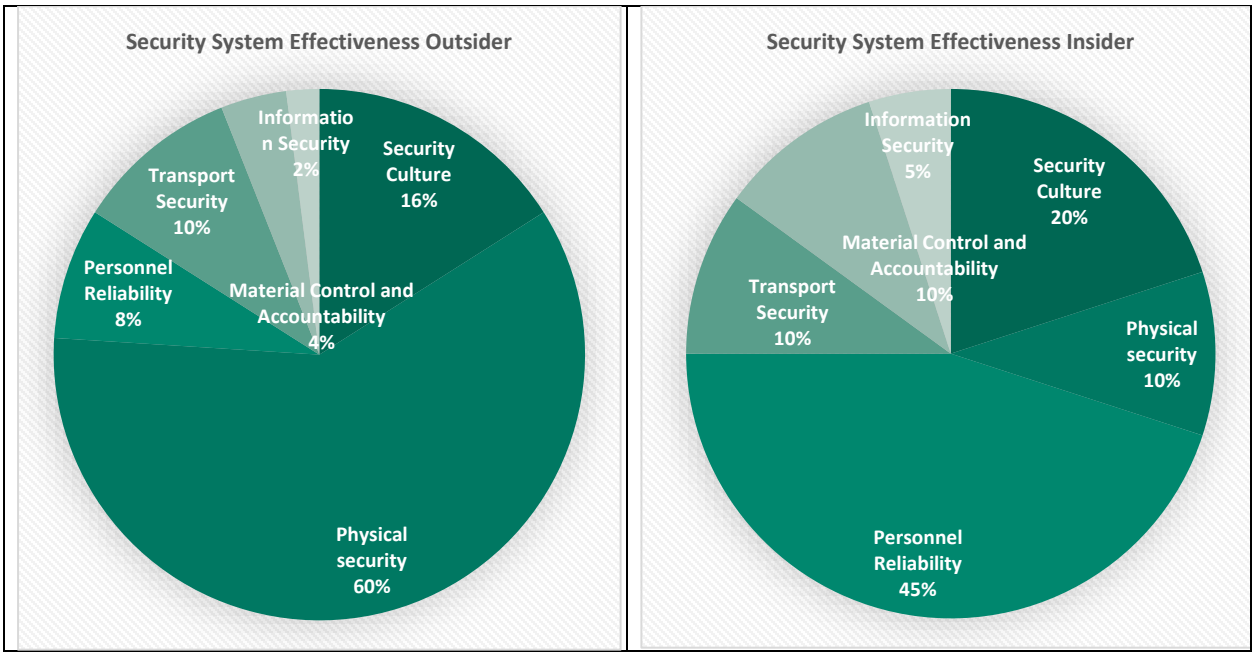


Figure 5: Weights for security system effectiveness – outsider and insider

For each question used to define the subtopics, the subject matter experts defined a question specific weight and ordinal values reflecting the various answer options. As such, the equation to define the P_E for the facility's security system is based on a weighted average of the answer values for each question and its associated weight. Separate question values are used to define the security system's effectiveness to outsiders and to insiders (P_{EO} and P_{EI}). Below are the two equations used to define consequences.

$$P_{EO} = \sum_{i=0}^{n} SOi, wi$$

Where SO is the value defined for each of the questions (*i*) under the security system effectiveness category defined to support protection against outsiders (those unauthorized to access the facility) and *w* is the defined weight for the question.

$$P_{EI} = \sum_{i=0}^{n} SIi, wi$$

Where SI is the value defined for each of the questions (*i*) under the security system effectiveness category defined to support protection against insiders (those with authorized access to the facility) and *w* is the defined weight for the question.

The following sections detail the specific questions under each of the security systems subtopics.

The security systems level of implementation is defined by a series of questions; whose answers are defined by a value. The tool provides discrete numbers reflecting the answer options; however, the user of the tool can answer any question with a continuous value between 0 and 1, but they should use the defined discrete values to help guide their final number. This value is then combined with the tool defined weight, these weighted values are then combined (as a weighted average) to create the overall scores defining P_E. Where the discrete values appear to jump – that is go from .1 to .25 to 1 – this reflects an SME defined non-linear value function.

2.2.1. Security Culture

The security culture of a facility (or laboratory) is critical to an effective security system. This culture is difficult to measure, but the commitment of management and awareness of security by the personnel of the facility help to define the exiting culture. In BioRAM, the security culture of a facility is measured based on actions that support the creation of a culture. These include documentation, training, and clear roles and responsibilities. These five questions are defined to reflect actions that would reflect a minimal security culture to those that would support a strong security culture. Below are the five security culture questions:

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
1. Does the institution have defined roles and responsibilities for biosecurity?	There is no identification of, or education on, biosecurity roles and responsibilities	Facility personnel are educated on their biosecurity roles and responsibilities	A biosafety officer is identified at this facility		Management at this facility ensures roles, responsibilities and authorities are defined, documented, and communicated
2. Has the institution made a commitment to security?	Management at this facility is not aware, or interested in, biosecurity concerns	Management at this facility is aware of biosecurity concerns, but has not implemented a biosecurity policy or devoted resources to address the issue	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	This facility has a comprehensive biosecurity 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 biosecurity system and communicates	Management at this facility identifies and prioritizes program needs and allocates funds as necessary

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
				this to all stakeholders.	
3. Does the institution have comprehensive biosecurity documentation?	This facility has no biosecurity policies, manuals, or SOPs	This facility has no specific biosecurity documentation	This facility has some biosecurity documentation, but they are not comprehensive and / or not fully implemented	This facility has biosecurity policies, manuals, and SOPs	This facility's biosecurity documentation also includes risk assessment and incident response information
4. Does the institution conduct biosecurity drills or exercises?	This facility does not conduct any biosecurity exercises		This facility conducts tabletops or other exercises on an ad hoc basis	This facility conducts annual exercises	This facility includes external responders in their exercises
5. Does the institution periodically review the biosecurity program?	There is no review of the biosecurity program	The biosecurity program is reviewed and revised as necessary after any incidents or near-incidents		The biosecurity program is subject to internal self-assessments	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.

2.2.2. Physical security

Physical security criteria are based on the principles of detecting an unauthorized entry, delay of the unauthorized entity, assessment of the entity, and a response to the entry. The performance requirements for physical protection are based upon deterring theft of the biological material, or for higher risk biological materials, containing an adversary prior to their leaving the facility with the stolen material.

Physical protection system requirements should include defining a graded approach to security with the first layer protecting the storage (material security layer) or laboratory (room security layer) where the material is housed with and working outward to the building (building security layer) and finally the institutional perimeter (perimeter security layer).

- **Material security layer** includes the storage areas for the biological material (e.g. freezers, culture collections etc.) This layer acts as a deterrent to persons with both authorized and unauthorized access. Material security layers may require measures to support delay, detection, assessment, and the opportunity for response when warranted by the risk. Material security can also help support safety by limiting those who have access.
- **Room security** layer acts a deterrent to persons unauthorized for entry into the room and may require measures to support delay, detection, assessment, and the opportunity for response when warranted by the risk. Room security can also help to support safety by limiting those who have access to the biological material. An enclosed fence or "cage" within a larger space could offer the same level of security as room security.
- **Building security** is used as a deterrent to outsiders and may require measures implemented to support delay, detection, assessment, and the opportunity for response when warranted by the risk.
- **Perimeter security** is used as a deterrent to outsiders, and may require measures implemented to support delay, detection, assessment, and the opportunity for response when warranted by the risk. A perimeter can also support the creation of a security culture. The perimeter does not specifically protect the material.

The physical protection system also considers the measures used to control access into the various layers. Controlled access supports differentiating between those with authorized access and those without. The tool has 10 questions used to characterize a facility or laboratory's physical security system. The weights for those differ in considering the effectiveness of the system against someone without authorized access to the facility (outsider) and someone with authorized access (insider). Below are the relative levels of importance of each question at defining the physical security systems' effectiveness for each of those potential adversaries. From these figures, the impact of a barrier is important for outsider protection but has no impact on insider protection.

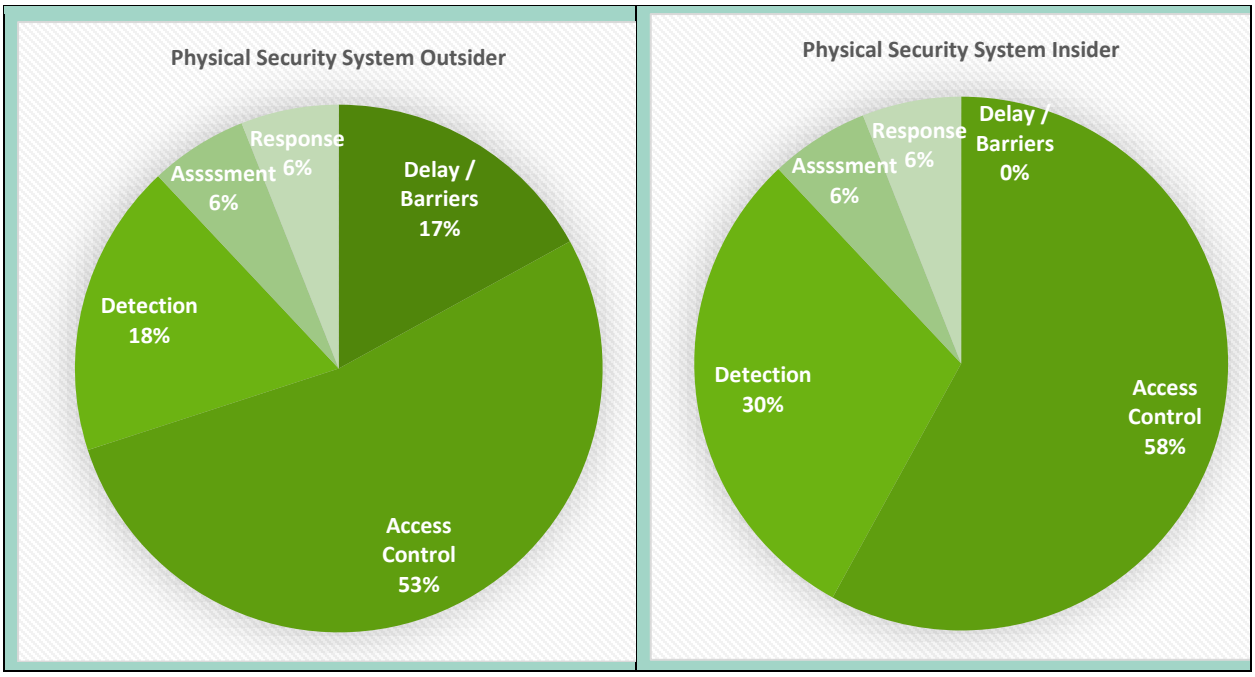


Figure 6: Relative weights for the elements of a physical security system

2.2.2.1. Delay

The following questions evaluate barriers, or delay measures, that exist between the exterior of the facility and the biological material. As mentioned in the introduction, these are evaluated based on what they do, and the tool is not specifically defining methods (such as chain link fence) to define these barrier measures.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.75	Discrete Answer Value =1
1. What type (if any) of a perimeter security exists outside the building(s)?	Facility has no perimeter	Facility has a partial perimeter	Facility has a clearly defined perimeter (natural or man-made)	
2. How many barriers exist between public areas and the biological agent?	Only a single barrier exists between public areas and the biological agent (e.g. a single door)			Multiple physical barriers exist between public areas and the biological agent

This question (1.) asks about the completeness of a perimeter surrounding the facility, a perimeter helps support deterrence and provides a defined boundary for the facility. As a biosecurity foundational expert once said, "No one accidently climbs an 8' fence". The question spans from no perimeter to a clearly defined perimeter that provides a strong delay (e.g. takes a long time to get over or through). This question (2.) considers the number of protection layers between public areas and the biological material of interest. This again does not require a prescriptive number but

captures this data solely because a single barrier offers little delay and multiple barriers offer more delay. As a side note - a door or a window that is not locked is not a barrier. As such, if at a facility, the public is allowed access to the building and the laboratory housing the biological material or doors and access points are not locked, there are **no barriers** between public areas and the biological material. A locked door on the laboratory would provide one barrier.

In answering this question, the users need to use their expertise on the effectiveness of barriers at their facility, this value should be scaled accordingly.

2.2.2.2. Access Control

Access control measures can be defined as those measures that allow someone with authorized access entry into the area. Since entry into an area is limited based on detection, delay, and response – access control measures create a by-pass for this security system. Access control systems are measured based on the principles of levels of authentication factor rather than the mechanism. This aligns with the performance concepts used across the BioRAM tool. A single factor authentication measure could be a single measure such as something you have (e.g. a key or a badge), something you know (e.g. pin number) or something you are (e.g. fingerprint). Multiple factors (having more than one of these three) provides a higher level of authorization or trust than the individual entering has authorized access. In the BioRAM tool, procedural control offers only a low level of control, manual controls offer more control, and electronic measures that require multi-factors, are the best options defined in BioRAM.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
3. Does the building housing the select biological agent or toxin limit access through a control system when the building is not occupied?	Building has no access controls	Building has only procedural access controls	Building has manual access controls (keys and locks)	Building has electronic access controls based on something single authentication system (e.g. swipe card or biometric)	Building has electronic access controls based upon multiple factors for authentication (e.g. PIN and/or swipe card and/or biometrics)
4. Does the room housing the select biological agent or toxin limit access through a control system when the room is not occupied?	Room has no access controls	Room has only procedural access controls	Room has manual access controls (keys and locks)	Room has electronic access controls based on something single authentication system (e.g. swipe card or biometric)	Room has electronic access controls based upon multiple factors for authentication (e.g. PIN and/or swipe card and/or biometrics)

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
5. Do the select biological agents or toxins storage areas (freezers, culture collection, etc.) limit access through a control system?	Storage areas have no access controls	Storage areas have only procedural access controls	Storage areas have manual access controls (keys and locks)	Storage areas have electronic access controls based on something single authentication system (e.g. swipe card or biometric)	Storage areas have electronic access controls based upon multiple factors for authentication (e.g. PIN and/or swipe card and/or biometrics)
6. Are ALL individuals with access to the room, work areas, and any storage areas where select biological agents and toxins exist specifically approved for access?	No access controls exist on rooms or storage areas	Procedural access restrictions exist	Procedural access restrictions exist and individuals with access have been registered and approved		Electronic access controls, tied to a person, exist and individuals with access have been registered and approved.

Questions three to five (3. – 5.) specifically define the measures implemented to limit access starting at the building and ending with the biological material long-term storage areas. Question six (6.) links the facility procedures for authorizing access to the physical measures that control access.

2.2.2.3. Detection

One of the key theories regarding security systems is that adequate security performance emerges from actively observing and proactively responding to security risk, and the measures defined to detect unauthorized access support this active observation. BioRAM is not measuring the effectiveness, diversity, redundancy, or other formal metrics regarding detection and communication, but rather is capturing the existence of detection measures. As with delay, the user should use their expertise regarding the effectiveness of the facility's detection system in these values.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
7. Do intrusion detection systems exist in the areas where	No intrusion detection	Only detection is staff trained to report anything unusual	Detection based on observations by personnel, including roving guard patrols	Local annunciation of alarms only	Alarms for intrusion detection are reported to a guard station

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
select biological agent or toxins are used or stored?					located within the facility or campus
8. Are ALL doors (or other potential entry points) covered by an intrusion detection system?	No controls (access controls and/or intrusion detection) on any entry points			Control only on doors	Controls on all possible entry paths through barrier (e.g. glass break sensors on windows)

Question seven (7.) is measured considering values that range from the areas where biological material is used or stored having no intrusion detection, to procedural detection measures, to robust detection systems trigging alarms that are communicated and assed by responders (e.g. onsite guards). Question eight (8.) focused on detection of unauthorized entry. This can link to an electronic access control system depending on the system configuration.

2.2.2.4. Response

The final two questions under the physical security section are focused on response to an alarm, witnessed unauthorized access, or suspicious actions. Response is characterized by the operational processes following activation of an alarm. These also include the considerations regarding who is responsible for the response (internal or external response).

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
9. How are alarms assessed?	No alarm assessment	Only alarm assessment is staff trained to report	Guards sent to assess alarms	Alarm assessed by camera	Alarm assessed by camera that records brief time before alarm and then afterwards
10. How are alarms responded to?	No plans for alarm response		Local law enforcement is initial response and a MOU is in place for this	Local law enforcement is initial response, MOU in place, and this is exercised regularly OR Onsite guard response	Onsite guard response and LLE back-up with MOU and regular exercises

2.2.3. Personnel Reliability

The performance requirements for defining persons who legitimately have access to the biological materials should be based upon the risks posed by the specific biological materials and the needs of the facility/laboratory/institution. The requirements should consider measures to determine if a person has been properly trained in safety, use of personal protective equipment, use of equipment, entry and exit procedures, etc.; training in the responsible use of biological materials; and has been provided information regarding the risks posed by the biological materials (for example, has reviewed and understood the material safety data sheets). Measures should also include processes to determine the level of integrity of the person; these can include verification of education and past employment and, when warranted, can include formal background checks.

The requirements for access to the biological materials should also consider the processes for visitors (short- and long-term) to the facility or institution, the process for changing access credentials following a person's departure (long-term departure) from the facility, and how access will be controlled and supported through procedures and, when required, electronic or key access control systems. BioRAM captures information related to what personnel reliability measures exist based on questions that focus on vetting procedures, visitor control, identification measures via badging, training of staff, and finally measures that support individuals. The processes for physical control regarding access to the biological material is included as part of the defined physical security. Personnel reliability, as reflected on Figure 5, is not relevant in the security against outsiders, but is significant in measuring the level of effectiveness of the security system at reducing the vulnerabilities of a facility against those with authorized access.

2.2.3.1. Vetting

Vetting are procedural controls that help to determine the integrity of those with authorized access to the biological material or the facility itself. There are various methods for vetting, but ideal methods include verification of credentials, references, criminal history, and additional checks for derogatory information (e.g. financial checks, drug screening, interviews of contacts, personality tests) and regular reevaluation intervals are established. These are evaluated considering those with direct access to the biological material and those who have facility or laboratory access, but not specific access to the biological material.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
1. How are personnel vetted prior to allowing them unescorted access to the agent?	No vetting of personnel prior to granting access	Vetting includes only verification of credentials (education, prior employment) and references	Vetting includes verification of credentials, references, and criminal history	Vetting includes verification of credentials, references, criminal history, and additional checks for derogatory information (e.g. financial checks, drug screening, interviews of contacts,	Vetting includes verification of credentials, references, criminal history, and additional checks for derogatory information (e.g. financial checks, drug screening, interviews of contacts,

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
				personality tests)	personality tests) and regular reevaluation intervals are established
2. How are the personnel vetted who will not have direct access of the agent?	No vetting of personnel prior to granting access	Vetting includes only verification of credentials (education, prior employment) and references	Vetting includes verification of credentials, references, and criminal history	Vetting includes verification of credentials, references, criminal history, and additional checks for derogatory information (e.g. financial checks, drug screening, interviews of contacts, personality tests)	Vetting includes verification of credentials, references, criminal history, and additional checks for derogatory information (e.g. financial checks, drug screening, interviews of contacts, personality tests) and regular reevaluation intervals are established

2.2.3.2. Visitor Control

There are many types of visitors who frequent facilities housing biological materials. Visitors may include research partners, patients, janitorial staff, equipment repair, personal, etc. BioRAM does not specifically review the procedures for all visitors but considers the processes related to escorting visitors who have been authorized direct access to biological materials. Escorting is the process where someone with authorized access oversees those without authorized access while they are in the room housing or potentially working with the biological material.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
3. How are visitors and other individuals who have not been vetted escorted when accessing rooms with the biological agent	Allowed unescorted access to room with asset	Administrative escorting to room with asset allowed	Escorting requirements in place but not defined escort ratios	Escorting requirements in place and escort ratios defined	Escort ratios defined; dates/times of escorted visitors recorded

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
or other materials?					

2.2.3.3. Badging

Badges support a security culture by detecting or recognizing unauthorized individuals by others. Where access control systems are based on electronic systems, the badges are a tangible item the authorized person must have to gain access to specific buildings, rooms, or storage devices. These questions consider the existence of badges by persons with authorized access, the contents of the badges, and the procedures surrounding a facility's use of badges.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
4. Are badges worn?	No				Yes
5. Do badges indicate level of access allowed by the wearer?	Badges not required or routinely worn or badges that are worn do not identify if badge belongs to person wearing it				Badges have a photo and expiration date
6. Does badge include a photo of the wearer (owner) and a time interval for when it is valid?	Badges not required or routinely worn	Badges are periodically but there are no formal procedures or requirements for photos to be on the badge	Badges contain a photo of the wearer or are specifically marked for visitors or other individuals needing temporary badging	Badges contain photo of the wearer	Badges contain photo of the wearer and a formal expiration date visible on the badge
7. Are there procedures for returning badges or reporting lost badges?	Badges not required or routinely worn Or there are no formal badge procedures				Procedures are in place for lost badges and turning in badges when access in no longer needed

The first badging question (4.) simply asks if badges are worn or not by those with authorized access. The BioRAM user should consider if badges exist but are not actually worn by those while

on site – in this case the value should be set to 'no'. The next questions (5. & 6.) focus on what information about the wearer the badges contain, such as if the badge is labeled or color-coded to reflect areas where the wearer is allowed or not allowed and the use of a photo so the badge is less susceptible to theft and covert use by an unauthorized person. The final question under badging (7.) reflects the procedures for badge management of a facility. This question focuses on ensuring lost badges are reported and needed access is removed for a lost badge. Similarly, if someone no longer requires access, their badge should be returned. Badge management should be considered for visitors also.

2.2.3.4. Training

Training under personnel reliability links back to the security culture of a facility. This training question specifically considers who receives specific biosecurity training.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
8. What is the level of biosecurity training provided?	No biosecurity training provided		Biosecurity training provided to anyone with unescorted access	Biosecurity training provided to all employees	Biosecurity training provided to all employees and on-site contractors (e.g. guards)

2.2.3.5. Employee assistance

The final question under personnel reliability focuses on employee assistance. These are measures that reduce the risk of someone with authorized access becoming susceptible to recruitment or coercion by those with malicious intent.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
9. Do employee assistance programs exist?	No support systems in place	Informal support network among personnel	Formal employee assistance program in place	Formal employee assistance program in place, and employees not penalized if access voluntarily suspended due to a temporary situation	Formal employee assistance program in place, and employees not penalized if access voluntarily suspended due to a temporary situation, plus there is an anonymous whistleblower / ombudsman type program in mechanism in place

The values defined for question nine (9.) reflect processes at the facility ranging from informal support mechanisms to a formalized and robust employee assistance program.

2.2.4. Transport Security

During movement of biological materials within and between facilities or institutions, the level of security for the transport should be consistent with the requirements defined for the security of the material within the facility. There may be limitations during transport, but the performance requirements for the physical protection system and for defining the persons involved in the transportation should be equivalent (when possible).

Considerations should include when and how biological materials are transported and how they are stored and secured between movements. A facility should specifically confirm the level of risk management processes for any facility biological materials are being supplied to. This will help to reduce the potential for a safety or security incident at the recipient site. When warranted, a formal chain of custody should be considered.

2.2.4.1. Internal transport controls

The first set of questions under the Transport section focus on the processes and procedures for materials transporting within the facility. These include understanding the level of physical security, personnel security, and administrative controls. For materials moving within a facility, the physical and procedural controls – including who has access – should align with the controls used while the material is being stored.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
1. What is the level of control at a facility of materials moving between laboratories or while in shipping/receiving areas?	No controls during internal transport	Agent transported by authorized individual but may be left unattended in unsecured areas		Agent not left outside of custody of authorized individual during transit unless secured but level of security is lower than how it is secured in storage	Agent not left outside of custody of authorized individual during transit unless secured in a manner equivalent or better to how it is secured in storage
2. What type of vetting is required for personnel transporting material within the facility?	Facility personnel who have access to materials during internal transport are not vetted		Facility personnel who have access to the materials during internal transport are vetted but to a lower degree		Facility personnel who have access to materials during internal transport are vetted to the same degree or

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
			than those who handle the agent in the laboratory		better as personnel who handle the agent in the laboratory
3. What type of administrative approvals is required for internal transport?	No approvals or documentation required for internal transport		Pre-approval not required for internal transport, but transfer is documented in laboratory records		Pre-approval required for internal transport and the transfer is documented in laboratory records

The first two questions under transport (1. & 2.) ask specifically if the requirements and implemented measures align with that of the material while in storage. The third question (3.) is focused on the internal processes for approval before movement.

2.2.4.2. External transport controls

Once the biological material has left a facility, it is out of the facility's control. BioRAM is not including questions in detail regarding the security of the material in transit or upon receipt, however it does consider the processes and procedures to ensure the most appropriate actions are in place prior to biological material leaving a facility.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
4. What type of administrative approvals is required for external transport?	No approvals or documentation required for external transport	Pre-approval not required for external transport, but transfer is documented in laboratory records		Pre-approval by a responsible individual at the facility required prior to shipping to external recipient	And a material transfer agreement is required prior to final approval or an external regulatory body must approve the transfer prior to shipment
5. What is the required security level for the receiving facility when sharing this agent?	No biosecurity (or biosecurity status is unknown) at receiving facility		Receiving facility has biosecurity but their level of security is	Receiving facility has equivalent or better biosecurity	And notifications between shipping and receiving facility at time

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
			lower than at shipping facility		of dispatch and receipt, respectively
6. How are agents packaged for external transport?	Agent can be identified by examining labels on outside of the package				Conforms to infectious substance shipping labeling requirements but does not identify the specific agent on the outside of the package.
7. How are external carriers selected?	No thought is given to security in selection of carrier		External carrier chosen that has good reputation for security of commercial shipments (e.g. FedEx, DHL, Airborne Express)		External carrier chosen that has good reputation for security of commercial shipments (e.g. FedEx, DHL, Airborne Express) And the carrier has a security plan in place that covers shipments of dangerous biological agents

2.2.5. Material Control and Accountability (MC&A)

A biological material inventory should be a comprehensive system for defining what materials are in a facility, where they are located, how they are secured, and who is accountable for their management (safety and security). The creation of a comprehensive inventory system may be necessary to fully track the biological materials in a facility, laboratory, or institution and to manage processes for safe and secure handling of these materials.

An inventory system will also support and help to sustain a biosecurity program. An inventory system can help reinforce good laboratory practices and will reduce the potential for materials to be orphaned or lost. Not all biological material requires the same level of detail in the inventory system; rather, a risk-based approach should be used to define the level of information required in the inventory for the various materials located at a laboratory. Considerations for the inventory may

include defining where different biological materials can be used and stored, how they are identified, and how the inventory is maintained. The person defined as accountable for the management of the biological materials should be the person best able to answer questions about the materials and to ensure biological materials are not orphaned. Note: BioRAM inventory questions are not about quantity of materials.

2.2.5.1. Inventory

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
1. How does the facility determine which materials are subject to material control and accountability (MC&A) measures?	No materials are subject to MC&A measures	Individual PIs/lab owners make decisions about which materials require MC&A measures	Facility just relies on regulatory or international lists (e.g. Select agent list, Australia Group list) to determine which materials at their facility need MC&A measures	Facility risk assessment to identify and categorize those materials and forms of materials that require MC&A measures	Facility risk assessment to identify and categorize those materials and forms of materials that require MC&A measures and, where applicable, proactive measures towards the reduction of risk through elimination, substitution or minimization of volumes/quantities of agents, and the type and number of manipulations conducted.
2. Which materials are inventoried?	No material cataloging	Seed stock inventory electronically managed	Seed stock inventory actively managed and working stocks, including infected animal status, tracked through laboratory notes	Seed stock inventory electronically managed using a secure system and includes tracking of samples that have been transferred into and out of the lab, source, strain, controlled substance identification, form, responsible individual, etc.	Seed and working stock containers bar coded or otherwise identified, marked, and cataloged for inventory tracking purposes.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
3. What is the level of control of agents while in use (working stocks, infected animals, etc.)?	No controls in place when materials are in use		Controls in place when materials are in use (e.g. working tissue cultures, animals subjected to challenge experiments, in equipment such as incubators and centrifuges, etc.) but at lower level than controls for material in storage		Controls in place when materials are in use (e.g. working tissue cultures, animals subjected to challenge experiments, in equipment such as incubators and centrifuges, etc.) at equivalent level to controls for material in storage

The first question under MC&A (1.) considers the policies and procedures regarding a facility's inventory management. Ideally, these assume the facility has conducted a risk assessment to identify and categorize which biological materials require MC&A measures and, where applicable, proactive measures towards the reduction of risk through elimination, substitution or minimization of volumes/quantities of agents, and the type and number of manipulations conducted. The second question (2.) is a bit more specific regarding what biological materials are included in the inventory and how the inventory system is controlled. The final inventory question (3.) considers the procedural controls implemented during the life of the biological while at the facility.

2.2.5.2. Roles and Responsibilities

The final two questions under MC&A are focused on accountability, specifically the roles, responsibilities, and procedures regarding biological material control. BioRAM is not evaluating MC&A specific procedures as those should be unique to the facility, but rather on the intent of the procedures and the implementation of them within the culture of the facility.

Question	Discrete Answer Value = 0	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
4. Are there clearly defined accountability roles	No designation of responsibilities	PI aware of each agent used within their laboratory	A responsible individual is designated to	A qualified and vetted individual is designated to oversee the control

Question	Discrete Answer Value = 0	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
and responsibilities?			oversee the control of protected agents	of protected agents (agent-by-agent basis, on a per-laboratory basis, etc.)
5. Are there clearly defined procedures for material control and accountability (MC&A)?	No procedures for MC&A exist	Some MC&A procedures are in place, but they are not comprehensive and/or are not fully implemented		Written procedures are in place and implemented to ensure timely and accurate recording, reporting, and auditing of materials subject to MC&A measures

2.2.6. Information Security

The final section in the evaluation of the facilities security system is focused on information security. Information security involves procedural controls to protect information and the cyber security measures. Considerations for the protection of sensitive information should be implemented. Sensitive information would include information which could lead an adversary to theft or sabotage and help in their avoidance of any implemented security measures. Electronic as well as paper-based information should be protected.

2.2.6.1. Procedural controls on information

There are four questions that reflect the procedural controls (these are not in order within the BioRAM tool, so the question numbers presented below reflect the question numbers within BioRAM). These questions determine the types of policies present that help to define information as sensitive and processes to ensure its protection. These questions align with best practices regarding information management.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
1. Has information which is considered sensitive been clearly identified, marked, and protected at a level equivalent to the risk of loss or release?	Minimal Information Security	No identification and classification of information in place			Sensitive (security-related) information is identified, marked, and classified at a level equivalent to the risk

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
2. Is information which is considered sensitive protected from release or loss?	No protection of information		Some information protection procedures are in place, but they are not comprehensive and/or are not fully implemented		Protecting sensitive (security-related) information at a level equivalent to the risk (e.g. information considered an asset is held redundantly by the institution. Information is accessed on a need-to-know basis, by pre-approved/screened authorized individuals. Procedures for handling, storing, transmitting, and destroying sensitive information)
3. Are there clearly defined communication policies regarding sensitive information?	No communication policies exist		Staff is trained on communication policies		Means of communicating sensitive information is controlled (e.g. encryption for electronic transmission, no cellular discussions or communication /viewing sensitive materials).
5. Are there clearly defined policies for public disclosure of information?	No public disclosure procedures/policies in place		Some procedures/policies regarding public disclosure are in place but they are not comprehensive		Potentially sensitive (security-related) information is screened prior to public release, by an

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
			and/or are not fully implemented		established review and approval process. Modification of information to make it appropriate for public release

2.2.6.2. Cyber Controls

The final two questions [4 and 6] are based on the cyber security and the physical security of sensitive cyber assets. Cyber security includes measures implemented to reduce the risks of electronic attacks which can include disruption, release of information, or altering of sensitive information. The physical security of the informational assets (as with the security of the biological materials) reduces the potential for unauthorized access which may have similar results to an electronic attack.

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
4. Are electronic critical infrastructure systems (including inventory databases, alarm control stations, access control systems, building monitoring systems, etc.) protected from attack?	No protection (e.g. adversary can access the systems through the internet)		Basic good practices are in place (e.g. firewalls, desktop security)		Comprehensive IT security infrastructure in place or not applicable because no sensitive information is stored
6. Are electronic physical security systems (alarm control stations, access control systems, building	No protection (e.g. adversary can access the systems through the internet)	Systems are on the internal network by isolated from the internet by use of a firewall			Systems are on a private isolated network with no access from the internet or the general facility intranet

Question	Discrete Answer Value = 0	Discrete Answer Value = .25	Discrete Answer Value =.5	Discrete Answer Value =.75	Discrete Answer Value =1
monitoring systems, etc.) isolated from the public internet?					

2.3. Results

The results of all of the biosecurity questions described above are combined with the defined weights then aggregated to create a series of risk values. For biological materials that impact only humans or only animals, there are two risk values; for zoonotic materials there are four defined risk values:

- Risk of insider theft and misuse toward a human population
- Risk of outsider theft and misuse toward a human population
- Risk of insider theft and misuse toward an animal population
- Risk of outsider theft and misuse toward an animal population

Recall that in BioRAM, the probability of an attack, P_A, has been reflected to focus on the relative attractiveness of the biological facility as a theft target, based on having biological materials that are useful in the development of a biological weapon. The probability the security system will be effective against an attack, P_E, is based on the level of implementation of security measures to include physical security, transport security, cyber security, insider protection, and overall risk management of the laboratory. This value is inverted to reflect gaps in security. The consequences of attack, C, are defined in BioRAM as the human and/or animal health impacts following the use of the material as a biological weapon. The BioRAM tool reflects the overall risk as a two-dimensional function where $P_A \times (1-P_E)$ is reflected on one axis reflecting the theft potential and C reflecting consequences on the other.

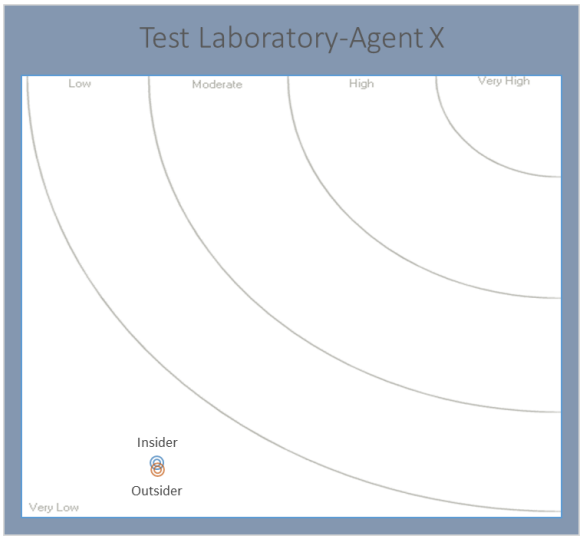
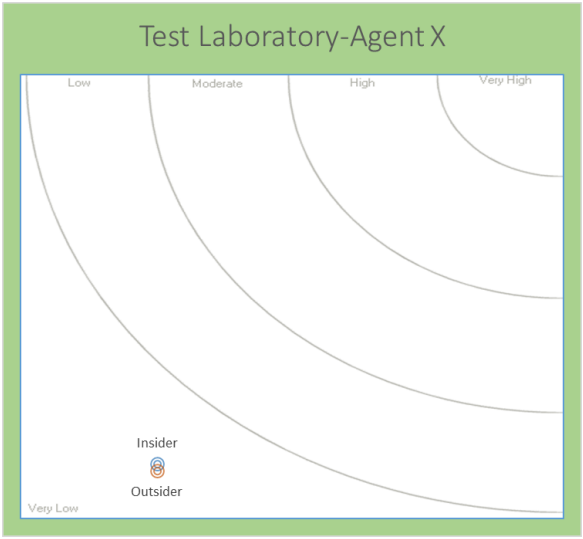
Biosecurity Risk of Agent X toward a human population	Biosecurity Risk of Agent X toward an animal population
	

Figure 7: Two-dimensional reflection of the probability of attack combined with the effectiveness of the security system against the attack (theft potential) (Y-axis) and the consequence of the attack toward humans and toward animals (X-axis) for "Agent X" housed at "Test Laboratory"

3. EXAMPLES, USE CASES, AND DISCUSSION

The following are examples of BioRAM use, additional discussions on some user questions, as well as some notes on user experiences.

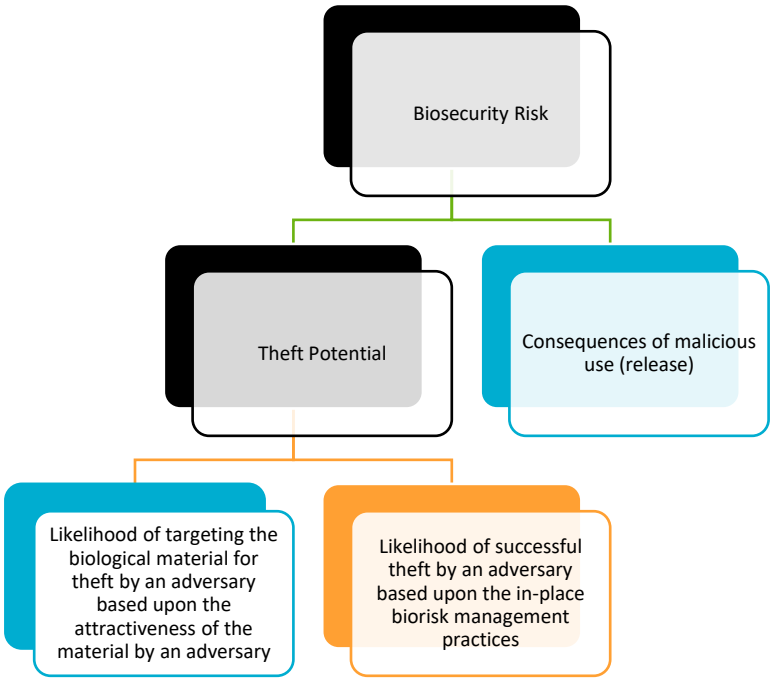


Figure 8: Biorisk Assessment Methodology

Recall, the BioRAM tool is organized into two top level topics, each with a series of subtopics and then, finally, the specific risk assessment questions. This portion of the guide will dive into each topic, sub-topic and the questions asked to outline the how each impacts the final risk (either negatively or positively) and the implications.

The topics include:

- Agent (the properties of the biological material) – boxes colored blue in Figure 2
- Facility (the level of implementation of security system measures) – boxes colored orange in Figure 2

3.1. Examples

These examples involve a research laboratory working with an isolate of *Bacillus anthracis* and an isolate of an influenza strain that mirrors the 1918 outbreak (Spanish Flu). The questions reflecting the security system's effectiveness are based a hypothetical laboratory setting.

3.1.1. *Properties of Bacillus anthracis*

3.1.1.1. Attractiveness questions

Attractiveness Question	Answer and Value
Utility of the material	
L1. What type of material will be used in this procedure?	Purified biological materials (stock culture) (Value of 1)
1. What is general population's knowledge or awareness of this agent as related to biological weapons or bio-crime?	Agent has a history of use in bioterrorism, bio-crime, or biowarfare (Value of 1)
2. What will the level of social impact (public panic, rioting, people being unwilling to go out and work, fear of additional incidents) of the disease caused by this agent occurring in the country?	The social impact of an agent release from the facility would be catastrophic (Value of 1)
Production	
3. What is the level of microbiological skill required to grow a suitable quantity (to meet the malicious objective) of this agent?	Production of a suitable quantity of this agent requires advanced technical skills (Value of .3) – can be challenging, but the technical skills are not novel, just require experience
4. What is the general accessibility of production equipment required to produce this agent?	Production equipment can be acquired or fabricated (Value of .75) – not easily acquired, but not abnormal for more laboratories
5. What are the storage requirements for this agent?	Agent is stable long-term without cold storage (Value of 1) – considering in spore form
Dissemination	
6. 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)?	This is a known infectious route (Value of 1)
6a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	No, the ID50 is greater than 1,000 (Value of .5 – this value is only zero if the parent route is also zero)
7. Is this agent known to cause infection via percutaneous exposure (to cause infection through compromised skin or direct injection into the blood stream)?	This is a possible infectious route (Value of 0.5)
7a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	No, the ID50 is greater than 1,000 (Value of .5 – this value is only zero if the parent route is also zero)
8. Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes)?	This is an infectious route (Value of 1)
8a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	No, the ID50 is greater than 1,000 (Value of .5 – this value is only zero if the parent route is also zero)

Attractiveness Question	Answer and Value
9. Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract)?	This is a known infectious route (Value of 1)
9a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	No, the ID50 is greater than 1,000 (Value of .5 – this value is only zero if the parent route is also zero)
10. 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))?	This is not an infectious route (Value of 0)
10a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	This is not an infectious route (Value of 0)
11. What is this agent's stability outside of a host?	Agent stable in the environment for months (Value of 1)
12. Can host to host transmission be used as a dissemination pathway to execute an attack?	No, disease does not transmit between hosts (Value of 0)

Based on these answers, *Bacillus anthracis* has an attractiveness value of .75 out of 1, which is a high value relative to other biological materials.

3.1.1.2. Consequence of malicious use questions

The following are the questions and answers reflecting the consequences of malicious use of a biological material to a human and to an animal. The questions highlighted in blue are human only questions, those in grey are animal only, and those unhighlighted are used in both final calculations.

Consequences	Answer and Value
Morbidity	
1. What is the duration of illness in a normal healthy human host?	Signs of illness present life of host (assuming untreated host and an inhalation exposure, the high potential of death is reflected in this value being 1)
2. What is the severity of illness in a normal healthy human host?	Extreme signs of disease, host requires mechanical assistance to sustain life, death imminent (assuming untreated host and an inhalation exposure, the high potential of death is reflected in this value being 1)
3. What is the duration of infection in a normal healthy human host?	Illness present life of host (assuming untreated host and an inhalation exposure, the high potential of death is reflected in this value being 1)
4. Does this disease cause any long-term conditions in a normal healthy human host?	No long-term impact (Value of 0)
Mortality	

Consequences	Answer and Value
5. What is the frequency of death (mortality rate) in humans caused by this disease?	High mortality (75% or more) (Value of 1)
Animal Impact	
6. If the agent infects animals, what is the expected morbidity rate to a naïve but otherwise healthy animal population?	High mortality (75% or more) (Value of 1)
7. What species of animals can this agent infect?	Affects multiple, significant agricultural species which are used for export and/or the by-products are a major source of protein for the country (Value of 1)
8. What is the disease impact on the general population?	Potentially affected animals are currently vaccinated for the disease caused by this agent (Value of 0) – in areas where anthrax vaccine is widely used
Socioeconomic	
9. What is the economic impact of an outbreak of this agent to the country?	The economic impact of an agent release from the facility would be catastrophic, significant impact to the GDP of the country. (Impacts of trade and tourism) (Value of 1) – this is driven mostly by the fear following a malicious use of this as compared to the impact of a natural outbreak
10. Is this agent endemic in the country?	The agent is not endemic in the country, but outbreaks have occurred (Value of .5) – this is the situation for this specific example
11. Are there active eradication/control programs of this agent in the country?	Control program is operational and is moderately effective (Value of .7) – this is the situation for this specific example
12. Are clinical signs strong indicators of disease present? (For example, diseases that cause sudden death or diseases with obvious signs will be detected faster.)	Significant Consequences presented with disease (Value of 1) – easier to detect also increases the optics of the disease
Mitigation Measures	
13. Are effective diagnostic tests available in the country for humans?	Yes (Value of 1) – this is the situation for this specific example
14. Are effective post exposure treatments (including immuno-globulin, vaccines and anti-microbials) available in the country for humans?	Yes (Value of 1) – this is the situation for this specific example
15. Are preventative measures (vaccines) available in the country for humans?	Yes (Value of 1) – this is the situation for this specific example
16. Are effective diagnostic tests available in the country for animals?	Yes (Value of 1) – this is the situation for this specific example

Consequences	Answer and Value
17. Are effective post exposure treatments (including immuno-globulin, vaccines and anti-microbials) available in the country for animals?	Yes (Value of 1) – this is the situation for this specific example
18. Are preventative measures (vaccines) available in the country for animals?	Yes (Value of 1) – this is the situation for this specific example
19. Are secondary consequence measures feasible in the country for animal populations?	Yes (Value of 1) – this is the situation for this specific example
Secondary Transmission	
Transmission	
20. How easily does this agent transmit between human hosts?	Disease does not transmit between hosts (Value of 0)
21. How easily does this agent transmit from animal to human hosts?	Disease does not transmit between hosts (Value of 0)
22. How easily does this agent transmit from human to animal hosts?	Disease does not transmit between hosts (Value of 0)
23. How easily does this agent transmit between animal hosts?	Disease does not transmit between hosts (Value of 0)
Routes	
24. 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?	This is a known infectious route (Value of 1)
25. 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?	This is a possible infectious route (Value of .5)
26. Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes) in the natural environment?	This is a known infectious route (Value of 1)
27. Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract) in the natural environment?	This is a known infectious route (Value of 1)
28. 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))?	This is not an infectious route (Value of 0)
29. 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)?	This is not an infectious route (Value of 0)

Consequences	Answer and Value
30. Is this agent known to cause infection via sexual transmission (to cause infection through sexual contact including intercourse)?	This is not an infectious route (Value of 0)

Using these values, the consequence values to humans results in a .73 score and for animals a .74 score which are both relatively high.

Bacillus anthracis risk

While not specifically included as part of the BioRAM results, the following is the results of the combined attractiveness of this biological material as an isolate and the consequences to humans and animals, if used maliciously.

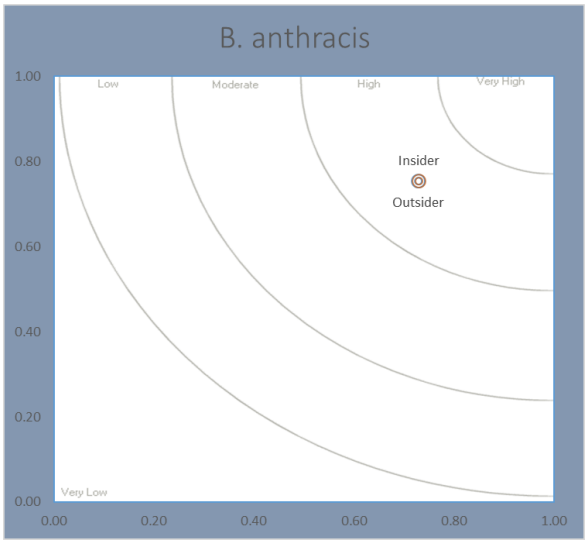
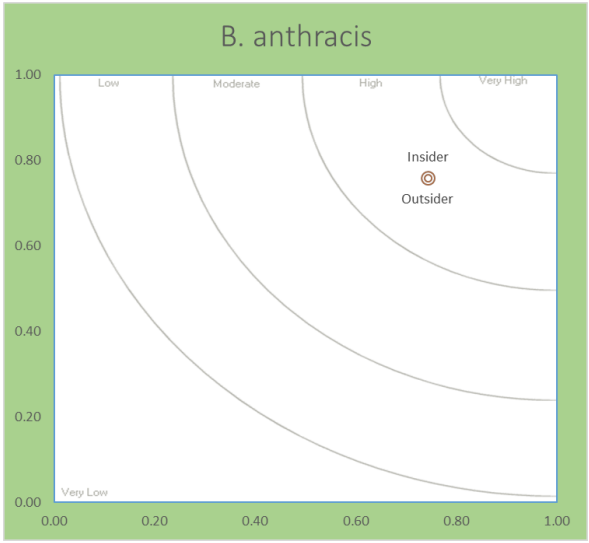
B. anthracis Risk if used against humans	*B. anthracis* Risk if used against animals
	

Figure 9 Risk of B. anthracis

These results highlight that an isolate of *B. anthracis* has a high risk and is therefore highly attractive for malicious use with a high relative level of consequences. These results do not consider the security measures that could reduce the potential access.

3.1.2. Properties of Reconstituted 1918 Influenza (Spanish Flu)

3.1.2.1. Attractiveness questions

Attractiveness Question	Answer and Value
Utility of the material	
L1. What type of material will be used in this procedure?	Purified biological materials (stock culture) (Value of 1.00)
1. What is general population's knowledge or awareness of this agent as related to biological weapons or bio-crime?	Agent has no history of use, but due to pandemic history and its inclusion as a controlled pathogen treated similar to does with a history of use (Value of 0.75)
2. What will the level of social impact (public panic, rioting, people being unwilling to go out and work, fear of additional incidents) of the disease caused by this agent occurring in the country?	The social impact of an agent release from the facility would be catastrophic (Value of 1)

Attractiveness Question	Answer and Value
Production	
3. What is the level of microbiological skill required to grow a suitable quantity (to meet the malicious objective) of this agent?	Production of a suitable quantity of this agent requires advanced technical skills (Value of 0.30)
4. What is the general accessibility of production equipment required to produce this agent?	Production equipment can be acquired or fabricated (Value of .75) – not easily acquired, but not abnormal for more laboratories
5. What are the storage requirements for this agent?	Agent is stable for days - weeks (Value of 0.30)
Dissemination	
6. 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)?	This is a known infectious route (Value of 1)
6a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	The ID is less than 1000 (Value of 1.00)
7. Is this agent known to cause infection via percutaneous exposure (to cause infection through compromised skin or direct injection into the blood stream)?	This is a possible infectious route (Value of 0.5)
7a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	The ID is less than 1000 (Value of 1.00)
8. Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes)?	This is a known infectious route (Value of 1)
8a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	The ID is less than 1000 (Value of 1.00)
9. Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract)?	This is a possible infectious route (Value of 0.5)
9a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	The ID is less than 1000 (Value of 1.00)
10. 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))?	This is not an infectious route (Value of 0)
10a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	This is not an infectious route (Value of 0)
11. What is this agent's stability outside of a host?	Agent stable only on interior surfaces for days to weeks (Value of 0.50)
12. Can host to host transmission be used as a dissemination pathway to execute an attack?	Yes (Value of 1.00)

Based on these answers, the Spanish Flu has an attractiveness value of .7 out of 1, which is a high value relative to other biological materials.

3.1.2.2. Consequence of malicious use questions

The following are the questions and answers reflecting the consequences (untreated) to a human and to an animal. The questions highlighted in blue are human only questions, those in grey are animal only, and those unhighlighted are used in both final calculations.

Consequences	Answer and Value
Morbidity	
1. What is the duration of illness in a normal healthy human host?	Multiple months to lifetime due to the high mortality rate (Value of 0.80)
2. What is the severity of illness in a normal healthy human host?	High signs of disease, host not able to function (hospitalized) (value of 0.80)
3. What is the duration of infection in a normal healthy human host?	Multiple months due to high mortality rate (Value of 0.80)
4. Does this disease cause any long-term conditions in a normal healthy human host?	Mild long-term impacts do not impede the hosts ability to function normally (Value of 0.25) – respiratory impacts
Mortality	
5. What is the frequency of death (mortality rate) in humans caused by this disease?	High mortality (75% or more) (Value of 1)
Animal Impact	
6. If the agent infects animals, what is the expected morbidity rate to a naïve but otherwise healthy animal population?	Medium mortality (15% to 74%) (Value of 0.60) – Swine based
7. What species of animals can this agent infect?	Affects multiple, significant agricultural species which are used for export and/or the by-products are a major source of protein for the country (Value of 1.00) – Swine based for a country that uses swine in their agricultural sector
8. What is the disease impact on the general population?	No current vaccination exists against this disease and animals at risk include young and others with compromised immune systems (Value of 1)
Socioeconomic	
9. What is the economic impact of an outbreak of this agent to the country?	The economic impact of an agent release from the facility would be catastrophic, significant impact to the GDP of the country. (Impacts of trade and tourism) (Value of 1.00)
10. Is this agent endemic in the country?	The agent is absent in the environment of the country (Value of 1.00)
11. Are there active eradication/control programs of this agent in the country?	Control program is operation and effective (Value of 1.00) – while no control program

Consequences	Answer and Value
	exists, the fact this is an eradicated pathogen it reflects an effective control program.
12. Are clinical signs strong indicators of disease present? (For example, diseases that cause sudden death or diseases with obvious signs will be detected faster.)	Significant Consequences (Value of 1.00)
Mitigation Measures	
13. Are effective diagnostic tests available in the country for humans?	No (Value of 1.00)
14. Are effective post exposure treatments (including immuno-globulin, vaccines and anti-microbials) available in the country for humans?	No (Value of 1.00)
15. Are preventative measures (vaccines) available in the country for humans?	No (Value of 1.00)
16. Are effective diagnostic tests available in the country for animals?	No (Value of 1.00)
17. Are effective post exposure treatments (including immuno-globulin, vaccines and anti-microbials) available in the country for animals?	No (Value of 1.00)
18. Are preventative measures (vaccines) available in the country for animals?	No (Value of 1.00)
19. Are secondary consequence measures feasible in the country for animal populations?	Yes (Value of 0.00)
Secondary Transmission	
Transmission	
20. How easily does this agent transmit between human hosts?	Agent can transmit between hosts easily (Value of 1.00)
21. How easily does this agent transmit from animal to human hosts?	Host to host transmission suspected (value of 0.50)
22. How easily does this agent transmit from human to animal hosts?	Host to host transmission suspected (value of 0.50)
23. How easily does this agent transmit between animal hosts?	Host to host transmission suspected (value of 0.50)
Routes	
24. 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?	This is a known infectious route (Value of 1)
25. Is this agent known to cause infection via percutaneous exposure (to cause infection through compromised skin or	This is a possible infectious route (Value of .5)

Consequences	Answer and Value
direct injection into the blood stream) in the natural environment?	
26. Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes) in the natural environment?	This is a possible infectious route (Value of .5)
27. Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract) in the natural environment?	This is a possible infectious route (Value of .5)
28. 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))?	This is a not an infectious route (Value of 0)
29. 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)?	This is a not an infectious route, but there is some concern (Value of 0.25)
30. Is this agent known to cause infection via sexual transmission (to cause infection through sexual contact including intercourse)?	This is a not an infectious route, but there is some concern (Value of 0.25)

Using these values, the consequence values to humans reflect a .93 and for animals a .95. This is very high relative risk.

3.1.2.3. 1918 Influenza risk

While not specifically included as part of the BioRAM results, the following is the results of the combined attractiveness of this biological material as an isolate and the consequences to humans and animals if used maliciously.

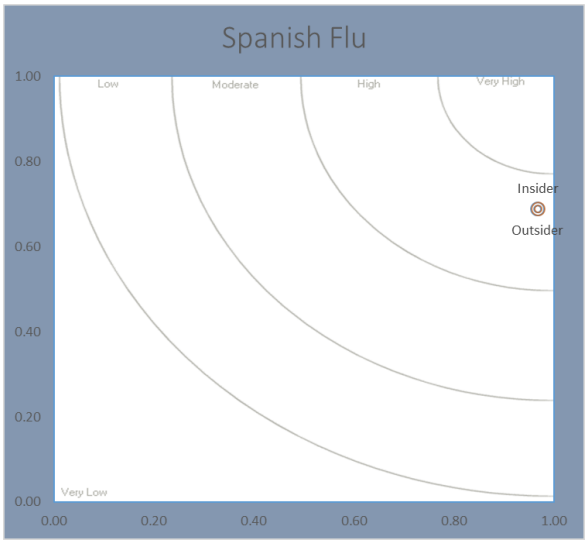
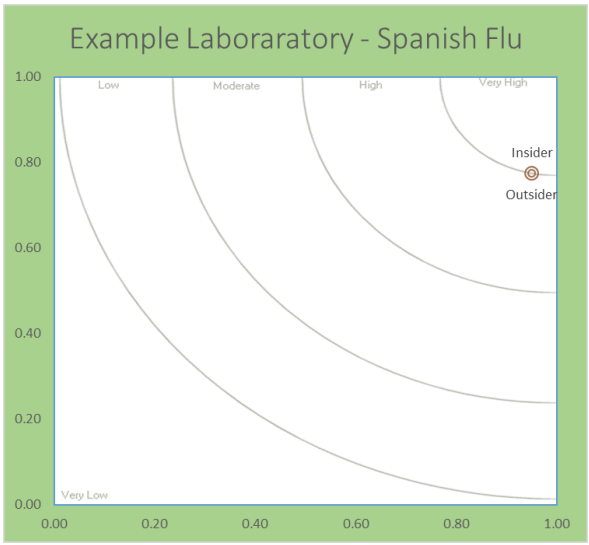
Spanish Flu risk if used against humans	Spanish Flu risk if used against animals
	

Figure 10 Risk of Spanish Flu

These results highlight that an isolate of the Spanish Flu has a high (almost very high) risk– it should be considered highly attractive for malicious use with a high relative level of consequences if the target is humans, and a low to moderate risk if the target was agricultural species. These results do not consider the security measures that could reduce the potential access.

3.1.3. Security System Effectiveness

For this example, the facility and specific laboratory will be defined mirroring an academic containment laboratory. The following table reflects the general measures used in the analysis and specifics will be reflected in the answers to the questions below. The defined security system should not be considered a listing of required or desirable measures of security, but simply provided to help users better understand software.

The laboratory's security system	The laboratory's safety system [1]
• Substantive management oversight and performance-management system in place • Documented, structured risk assessments – Security processes and procedures defined specifically by the risk assessments – Physical security elements designed and implemented based on the risk assessment	• Substantive management oversight and performance-management system in place • Documented, structured risk assessments – Mitigation measures (e.g. containment, PPE, waste handling, training) defined specifically by the risk assessments – There is active safety training for all with laboratory access • Containment system – BSC

[1] Not needed for the use of BioRAM security but included to help reflect on the full laboratory status

- There is active security training for all those with access to the laboratory
- Facility protection layers
  - The outer perimeter is defined as the building housing the laboratory
  - Doors are only locked after hours and weekend
  - The laboratory itself has a double door for entry, the outer door is locked with a manual key, the inner door is not locked, there are no functional windows in the laboratory
  - The freezer where isolates are stored in locked with a manual key
- Detection and Response
  - The building has door alarms and motion sensors which are active after hour with an attached sounder to alert guards
  - The laboratory has motion sensors which are active after hours with an attached sounder to alert guards
- Access Control Management
  - Keys are managed by the laboratory principal research, who assigns and tracks keys to both the building, laboratory, and freezer
  - Keys and access are given to students with approved research to be conducted within the laboratory, approvals are granted by the university's safety committee
  - Laboratory staff cleans laboratory themselves and escorts guests and maintenance personal
- Material Control
  - Isolates are tracked in an electronic inventory system that is
    - validated, documented procedures for use, cleaning, and maintenance
  - Directional airflow
    - validated, documented procedures for use, cleaning, and maintenance
- PPE
  - PAPRs
    - Specific training (including donning and doffing and storage), validated and documented procedures for use, cleaning, and maintenance
  - Gloves
    - Specific training (including donning and doffing and storage), validated and documented procedures for use and disposal
  - Gowns
    - Specific training (including donning and doffing and storage), validated and documented procedures for use and disposal
- Waste
  - Decontaminated in lab (validated and documented procedures)
  - Sharps housed in puncture resistant container, autoclaved, then incinerated
- Area
  - Surfaces solid, all watertight
  - Cleaning procedures validated and documented

maintained by the university's information technology center – Materials in the laboratory are considered 'owned' by the approved researcher and their responsibility for transfer or destruction following completion of the experiment • Research information is protected as proprietary until release for publication, but no other informational processes exist	

Security System Effectiveness	Answer and Value
Security Culture	
1. Does the institution have defined roles and responsibilities for biosecurity?	Yes, part of the biorisk management process implemented at this facility (Value of 1)
2. Has the institution made a commitment to security?	Yes, part of the biorisk management process implemented at this facility (Value of 1)
3. Does the institution have comprehensive biosecurity documentation?	Yes, part of the biorisk management process implemented at this facility (Value of 1)
4. Does the institution conduct biosecurity drills or exercises?	Yes, part of the biorisk management process implemented at this facility (Value of 1)
5. Does the institution periodically review the biosecurity program?	Yes, part of the biorisk management process implemented at this facility (Value of 1)
Physical security	
1. What type (if any) of a perimeter security exists outside the building(s)?	No, since open campus there are not specific perimeters outside of the building (Value of 0)
2. How many barriers exist between public areas and the biological agent?	There are two normally locked barriers (door and freezer) between the public and the isolates of anthrax (Value of .3)
3. Does the building housing the select biological agent or toxin limit access through a control system when the building is not occupied?	Building has manual access controls (keys and locks) (Value of .5)
4. Does the room housing the select biological agent or toxin limit access through a control system when the room is not occupied?	Room has manual access controls (keys and locks) (Value of .5)
5. Do the select biological agents or toxins storage areas (freezers, culture collection, etc.) limit access through a control system?	Storage areas have manual access controls (keys and locks) (Value of .5)

Security System Effectiveness	Answer and Value
6. Are ALL individuals with access to the room, work areas, and any storage areas where select biological agents and toxins exist specifically approved for access?	Procedural access restrictions exist and individuals with access have been registered and approved (Value of .5)
7. Do intrusion detection systems exist in the areas where select biological agent or toxins are used or stored?	Local annunciation of alarms only (Value of .7)
8. Are ALL doors (or other potential entry points) covered by an intrusion detection system?	Control only on doors (Value of .7)
9. How are alarms assessed?	Guards sent to assess alarms (Value of .45)
10. How are alarms responded to?	Onsite guard response and local law enforcement back-up (no formal MOUs between university and local law enforcement) (Value of .8)
Personnel Reliability	
1. How are personnel vetted prior to allowing them unescorted access to the agent?	Vetting includes only verification of credentials (education, prior employment) and references (Value of .2)
2. How are the personnel vetted who will not have direct access of the agent?	No vetting of personnel prior to granting access (Value of 0)
3. How are visitors and other individuals who have not been vetted escorted when accessing rooms with the biological agent or other materials?	Escorting requirements in place but not defined escort ratios (value of .45)
4. Are badges worn?	No (value of 0)
5. Do badges indicate level of access allowed by the wearer?	Badges not required or routinely worn or badges that are worn do not identify if badge belongs to person wearing it (Value of 0)
6. Does badge include a photo of the wearer (owner) and a time interval for when it is valid?	Badges not required or routinely worn (Value of 0)
7. Are there procedures for returning badges or reporting lost badges?	Badges not required or routinely worn or there are no formal badge procedures (Value of 0)
8. What is the level of biosecurity training provided?	Biosecurity training provided to all employees (Value of .7)
9. Do employee assistance programs exist?	Informal support network among personnel (Value of .2)
Transport Security	
1. What is the level of control at a facility of materials moving between laboratories or while in shipping/receiving areas?	Agent not left outside of custody of authorized individual during transit unless secured but level of security is lower than how it is secured in storage (Value of .7)
2. What type of vetting is required for personnel transporting material within the facility?	Facility personnel who have access to the materials during internal transport are vetted but to a lower degree than those who handle the agent in the laboratory (Value .45)

Security System Effectiveness	Answer and Value
3. What type of administrative approvals is required for internal transport?	Pre-approval not required for internal transport, but transfer is documented in laboratory records (Value of .5)
4. What type of administrative approvals is required for external transport?	Pre-approval by a responsible individual at the facility required prior to shipping to external recipient (Value of .7)
5. What is the required security level for the receiving facility when sharing this agent?	Receiving facility has equivalent or better biosecurity (Value of .9)
6. How are agents packaged for external transport?	Conforms to infectious substance shipping labeling requirements but does not identify the specific agent on the outside of the package. (Value of 1)
7. How are external carriers selected?	External carrier chosen has good reputation for security of commercial shipments (e.g. FedEx, DHL, Airborne Express) no knowledge of their security plan regarding biological materials. (Value of .5)
Material Control and Accountability	
1. How does the facility determine which materials are subject to material control and accountability (MC&A) measures?	Individual PIs/lab owners make decisions about which materials require MC&A measures (Value of .2)
2. Which materials are inventoried?	Seed stock inventory electronically managed (Value of .2)
3. What is the level of control of agents while in use (working stocks, infected animals, etc.)?	No controls in place when materials are in use (Value of 0)
4. Are there clearly defined accountability roles and responsibilities?	PI aware of each agent used within their laboratory (Value of .45)
5. Are there clearly defined procedures for material control and accountability (MC&A)?	Some MC&A procedures are in place, but they are not comprehensive and/or are not fully implemented (Value of .45)
Information Security	
1. Has information which is considered sensitive been clearly identified, marked, and protected at a level equivalent to the risk of loss or release?	No identification and classification of information in place (Value of 0)
2. Is information which is considered sensitive protected from release or loss?	Some information protection procedures are in place, but they are not comprehensive and/or are not fully implemented (Value of .5)
3. Are there clearly defined communication policies regarding sensitive information?	Staff is trained on communication policies (Value of .5)
4. Are electronic critical infrastructure systems (including inventory databases, alarm control stations, access control systems, building monitoring systems, etc.) protected from attack?	Comprehensive IT security infrastructure in place or not applicable because no sensitive information is stored (Value of 1) – University IT
5. Are there clearly defined policies for public disclosure of information?	Some procedures/policies regarding public disclosure are in place but they are not comprehensive and/or are not fully implemented (Value of .45)

Security System Effectiveness	Answer and Value
6. Are electronic physical security systems (alarm control stations, access control systems, building monitoring systems, etc.) isolated from the public internet?	Systems are on a private isolated network with no access from the internet or the general facility intranet (Value of 1)

This results in a security effectiveness value for this laboratory of a .48 regarding the protection against those with access and a .54 against those without access to the laboratory.

3.1.4. Results

The BioRAM tool combines the scores with the weights creating the final theft potential or likelihood value and the consequence value. The first results reflect the biosecurity risks for the laboratory isolate of *B. anthracis*. The second will reflect the relative biosecurity risks for an isolate of the Spanish flu.

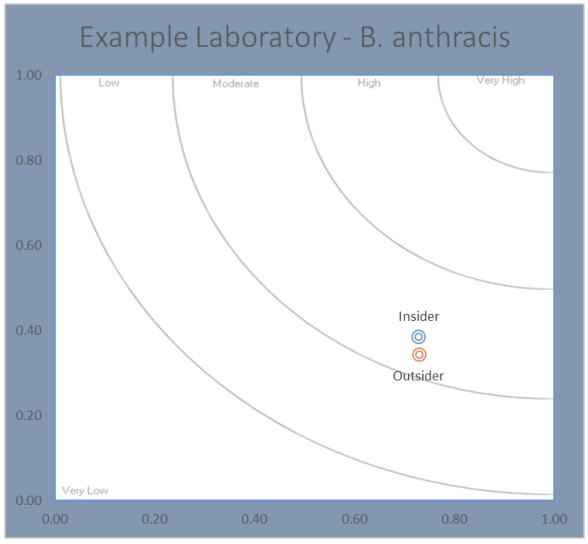
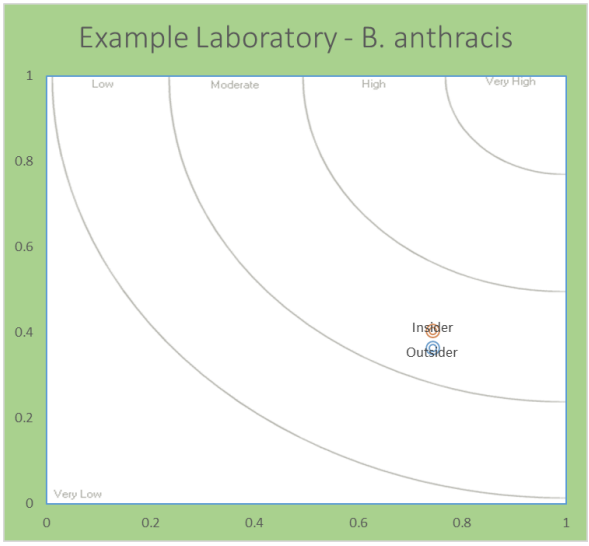
Biosecurity risk of *B. anthracis* toward a human population	Biosecurity risk of *B. anthracis* toward an animal population
	

Figure 11: Two-dimensional reflection of the probability of attack combined with the effectiveness of the security system from the example laboratory (Y-axis) and the consequence of the attack toward humans and toward animals (X-axis) a *B. anthracis* isolate

Based on the current security system and the properties of the biological material, the resulting relative biosecurity risks for the isolate of *B. anthracis* are considered moderate. Depending on the risk acceptance of the facility, this may be considered an unacceptable risk or maybe defined as an acceptable risk. Where defined as unacceptable, the facility should consider the implementation of additional security measures.

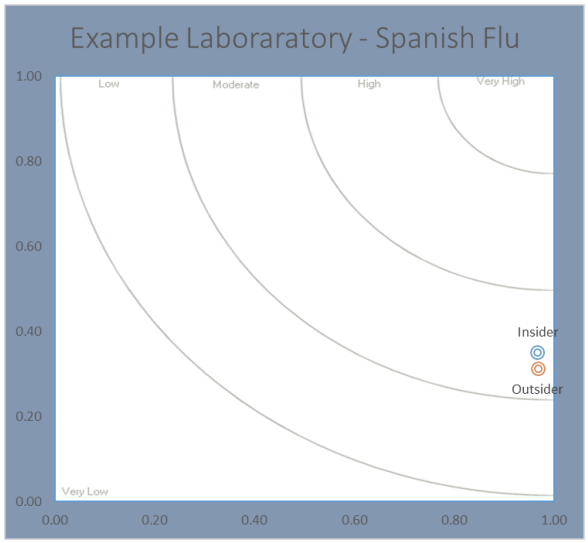
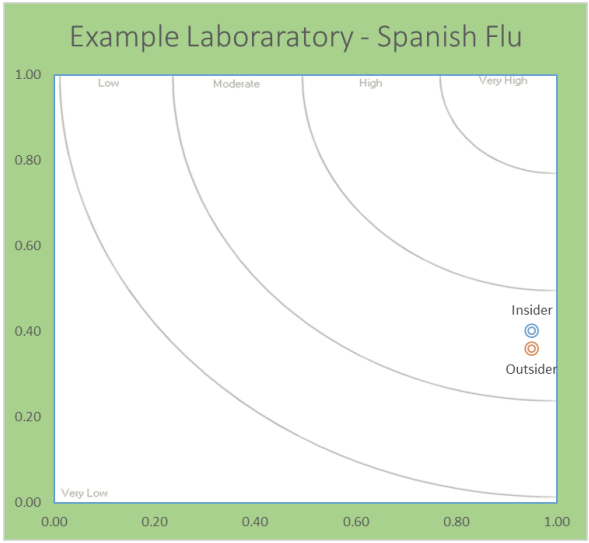
Biosecurity risk of Spanish Flu toward a human population	Biosecurity risk of Spanish Flu toward an animal population
	

Figure 12: Two-dimensional reflection of the probability of attack combined with the effectiveness of the security system from the example laboratory (Y-axis) and the consequence of the attack toward humans and toward animals (X-axis) a Spanish Flu isolate

Based on the current security system and the properties of the biological material, the resulting relative biosecurity risks for the isolate of Spanish Flu are considered moderate. Depending on the risk acceptance of the facility, this may be considered an unacceptable risk or maybe defined as an acceptable risk. Where defined as unacceptable, the facility should consider the implementation of additional security measures.

3.2. Special questions

Over the lifetime of BioRAM, the development team has received a handful of specific questions regarding the underlying philosophy of the model. The most common questions concern the impact of the facilities biosecurity risk with changing the access control measures (under physical security), and the difference in risk based on the different forms of the biological material of interest (e.g. environmental samples, tissue samples, or isolates).

The following sections will discuss these two examples in detail.

3.2.1. Access control

Recall that in BioRAM, access control measures are defined as those measures that allow someone with authorized access entry into the area. Since entry into an area is limited based on detection, delay, and response – access control measures create a by-pass for this security system. Access control systems are measured based on the principles of levels of authentication factor rather than the mechanism. This aligns with the performance concepts used across the BioRAM tool. A single factor authentication measure could be a single measure such as something you have (e.g. a key or a badge), something you know (e.g. pin number) or something you are (e.g. fingerprint). Multiple factors (having more than one of these three) provides a higher level of authorization or trust that

the individual entering has authorized access. In the BioRAM tool, procedural control as considered offering only a low level of control, manual controls offer more control and electronic measures that require multi-factors are the best options defined in BioRAM.

Access control is measured using five defined options ranging from a value of 0 – no access control, to 1 - reflecting multifactor access control:

- no access controls
- only procedural access controls
- manual access controls (keys and locks)
- electronic access controls based on something single authentication system (e.g. swipe card or biometric)
- electronic access controls based upon multiple factors for authentication (e.g. PIN and/or swipe card and/or biometrics)

Access control is measured at the building, room, and storage container separately. For this exercise, we will focus only on the impact of changing the room's access control mechanism. The examples provided will mirror the values from the example in section 3.1. The impact of the access control has a potential to change the overall security system effectiveness by 11% against outsiders and 3% for insiders. These are based on the SME defined weights within the model.

The following table provides the value reflecting the access control and the final security system effectiveness (insider and outsider) value.

Access Control of Room Housing Biological Material Value	Security Systems Effectiveness (P_E) Against an Insider	Security Systems Effectiveness (P_E) Against an Outsider
0. No Access Control	47%	49%
1. Only procedural access controls	48%	50%
2. Manual access controls (keys and locks)	50%	57%
3. Electronic access controls based on something single authentication system (e.g. swipe card or biometric)	50%	59%
4. Electronic access controls based upon multiple factors for authentication (e.g. PIN and/or swipe card and/or biometrics	50%	60%

The 3% change in insider effectiveness from no access to ideal (multiple factor) reflects the overall impact of access control on the security systems effectiveness against an insider as defined by the

SMEs. Similarly, the max change of 11% across the full range of measures reflects the SME defined impact of access control toward outsider protection. The individual scores for access control reflect a value function where the biggest delta is from procedural controls to manual control – reflecting that some types of locking is significantly better than no locking. There is a smaller increase from manual to electronic controls.

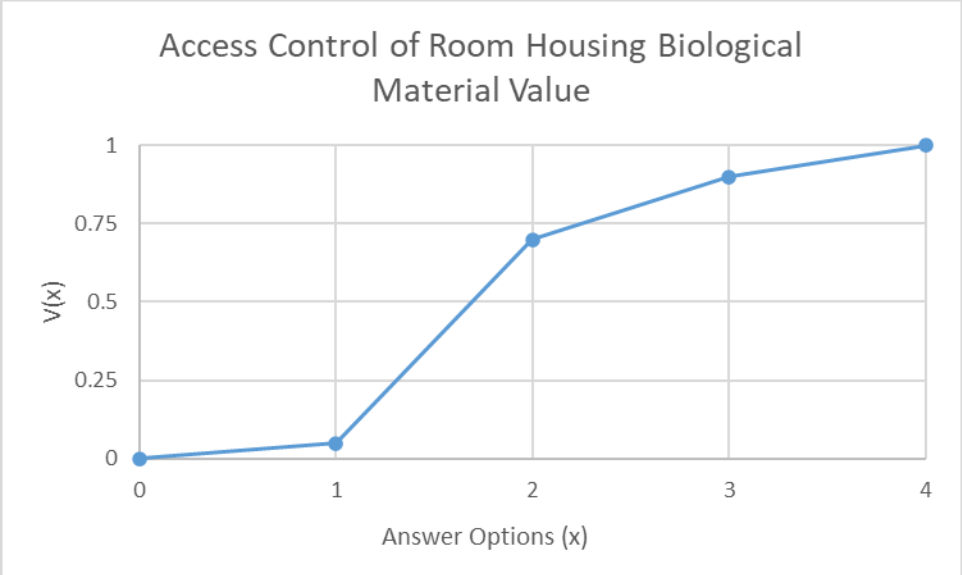


Figure 13: Value model used to reflect impact of access control

In the final risk value, this security system's effectiveness is combined with the attractiveness value reflecting the defined equation (P_A x (1-P_E)).

3.2.2. Type of material

The question that asks "what type of material will be used in this procedure?" is used to determine the value of the biological material to someone with malicious intent. It was determined by the biosecurity experts that an isolate is far more useful in developing a biological weapon than a diagnostic or environmental sample. The options within the model include:

- Environmental Samples (soil, water, etc.) = value of .1
- Diagnostic Samples (blood, urine, tissues samples, saliva, etc.) = value of .25
- Purified biological materials (stock culture) = value of 1

Using these values to reflect the biological materials attractiveness, the following table will provide the value reflecting the form of biological material and its attractiveness value. All other values used in this example mirror that of those defined in section 3.1 for *B. anthracis*.

Form of Biological Material	Overall attractiveness value
1. Environmental Samples (soil, water, etc.)	Value of .67

Form of Biological Material	Overall attractiveness value
6. Diagnostic Samples (blood, urine, tissues samples, saliva, etc.)	Value of .69
7. Purified biological materials (stock culture)	Value of .75

The range of .67 to .75 mirrors the SME defined overall weight of 8% of the form of the material in defining its overall attractiveness.

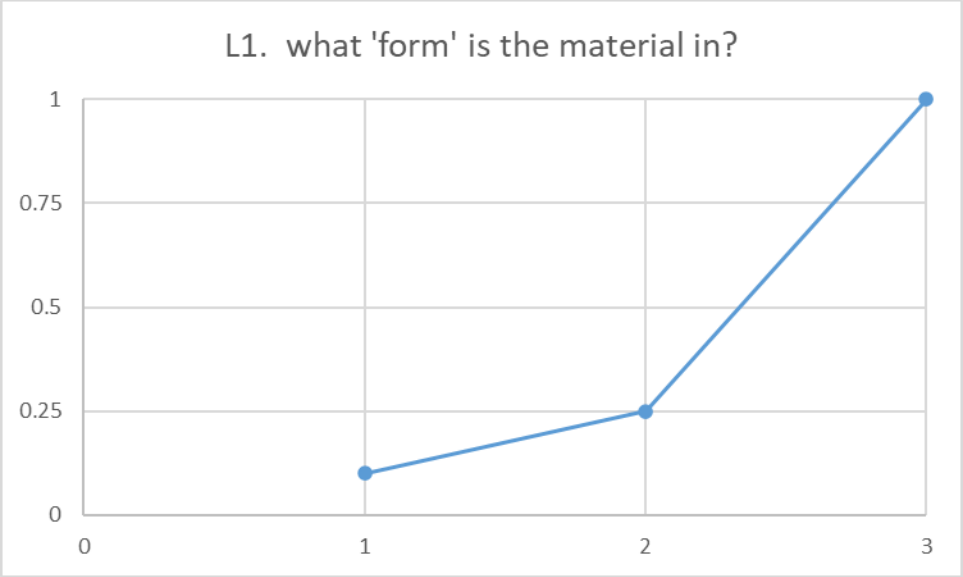


Figure 14: Value model used to reflect impact of the form of the biological material

In the final risk value, this attractiveness value is combined with the security systems effectiveness value reflecting the defined equation (P_A x (1-P_E)).

4. SUMMARY

BioRAM is being used across the globe for conducting risk assessment. The tool was initially peer reviewed by users from a diverse set of countries and types of laboratories. Some of the key advantages of using a process such as the BioRAM tool, highlighted from reviewer comments include:

- There is a notable time saving to using a structured process such as BioRAM and the tool itself is helps to ensure consistency between assessments
- The tool helps to ensure we are not reflecting our own biases into the assessment process
- The tool reflects the impacts of security measures based on expert opinion, helping to user to make decisions regarding mitigation implementation.
- BioRAM complies with the BioRisk management standard and supports meeting those objectives
- BioRAM make communication regarding risks more transparent and similar – for both communication to upper management and to support education of those working at the facility

The BioRAM tool will not replace expertise in security but has been designed to complement security expertise and help those experts in characterization and evaluation of security risks.

APPENDIX A. BIOLOGICAL MATERIALS WITH SME DEFINED VALUES INCLUDED IN BIORAM

- Abrin
- African Horse Sickness
- African swine fever virus
- Akabane virus
- Alastrim (Variola Minor Virus)
- Avian influenza virus (highly pathogenic)
- Bacillus anthracis
- Bluetongue virus (exotic)
- Botulinum Neurotoxin producing species of Clostridium
- Botulinum Neurotoxins
- Bovine spongiform encephalopathy agent
- Brucella abortus
- Brucella melitensis
- Brucella suis
- Burkholderia pseudomallei
- Burkholderia mallei
- Camel pox virus
- Central European Tickborne encephalitis
- Cercopithecine herpesvirus 1 (Herpes B virus)
- Classical swine fever virus
- Clostridium perfringens epsilon toxin
- Coccidioides posadasii/ Coccidiodes immitis
- Conotoxins
- Coxiella burnetii
- Crimean Congo haemorrhagic fever virus
- Diacetoxyscirpenol
- Eastern Equine Encphalitis virus
- Ebola Virus
- Ehrlichia ruminantium (Heartwater)
- Far Eastern Tick-borne encephalitis
- Foot-and-mouth disease virus
- Francisella tularensis
- Goat pox virus
- Hendra virus
- Japanese encephalitis virus
- Kyasanur Forest Disease
- Lassa fever virus
- Lumpy skin disease virus
- Malignant catarrhal fever virus
- Marburg virus

- Menangle virus
- Monkeypox virus
- Mycoplasma capricolum subspecies capripneumoniae
- Mycoplasma mycoides subspecies mycoides
- Nipah virus
- Omsk Hemorrhagic Fever
- Peronosclerospora philippinensis
- Peste des petits ruminants virus
- Phoma glycinicola
- Ralstonia solanacearum race 3 biovar 2
- Rathayibacter toxicus
- Reconstruction of the 1918 flu
- Ricin
- Rickettsia prowazekii
- Rickettsia rickettsii
- Rift Valley fever virus
- Rinderpest virus
- Russian Spring and Summer encephalitis
- Saxitoxin
- Sclerophthora rayssiae var zeae
- Sheep pox virus
- Shigalike ribosome inactivating proteins
- Shigatoxin
- Smallpox virus (Variola Major Virus)
- South American Haemorrhagic Fever Viruses:Flexal
- South American Haemorrhagic Fever Viruses:Guanarito
- South American Haemorrhagic Fever Viruses:Junin
- South American Haemorrhagic Fever Viruses:Machupo
- South American Haemorrhagic Fever Viruses:Sabia
- Staphylococcal enterotoxins
- Swine vesicular disease virus
- Synchytrium Endobioticum
- T-2 toxin
- Tetrodotoxin
- Venezuelan Equine Encephalitis virus
- Virulent Newcastle disease virus
- VSV (IN2, IN3 subtypes)
- Xanthomonas Oryzae
- Xylella Fastidiosa
- Yersinia pestis

APPENDIX B. BIORAM TOOL QUESTIONS AND WEIGHTS

B.1. Biological Materials

B.1.1. Attractiveness

Question	Weight
<u>Utility of the material for misuse</u>	
L1. What 'form' is the material in?	8.00%
1. What is general population's knowledge or awareness of this agent as related to biological weapons or bio-crime?	10.00%
2. What will the level of social impact (public panic, rioting, people being unwilling to go out and work, fear of additional incidents) of the disease caused by this agent occurring in the country?	6.00%
<u>Production</u>	
3. What is the level of microbiological skill required to grow a suitable quantity (to meet the malicious objective) of this agent?	10.00%
4. What is the general accessibility of production equipment required to produce this agent?	5.00%
5. What are the storage requirements for this agent?	5.00%
<u>Dissemination</u>	
6. 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)?	10.80%
6a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	3.00%
7. Is this agent known to cause infection via percutaneous exposure (to cause infection through compromised skin or direct injection into the blood stream)?	1.80%
7a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	3.00%
8. Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes)?	10.20%
8a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	3.00%
9. Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract)?	7.20%
9a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	3.00%
10. 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))?	4.20%
10a. Is the infectious dose (ID50) of this agent for this route less than 1000 or unknown?	3.00%
11. What is this agent's stability outside of a host?	4.80%

Question	Weight
12. Can host-to-host transmission be used as a dissemination pathway to execute an attack?	6.00%

B.1.2. Consequences

Question	Human Consequences Weight	Animal Consequences Weight
Health Impact		
Morbidity		
1. What is the duration of illness in a normal healthy human host?	2.59%	0.00%
2. What is the severity of illness in a normal healthy human host?	4.84%	0.00%
3. What is the duration of infection in a normal healthy human host?	1.13%	0.00%
4. Does this disease cause any long-term conditions in a normal healthy human host?	2.70%	0.00%
Mortality		
5. What is the frequency of death (mortality rate) in humans caused by this disease?	33.75%	0.00%
Animal Impact		
6. If the agent infects animals, what is the expected morbidity rate to a naïve but otherwise healthy animal population?		11.25%
7. What species of animals can this agent infect?		24.30%
8. What is the disease impact on the general population?		11.25%
Socioeconomic		
9. What is the economic impact of an outbreak of this agent to the country?	8.00%	6.40%
10. Is this agent endemic in the country?	4.00%	4.00%
11. Are there active eradication/control programs of this agent in the country?	2.00%	2.00%
12. Are clinical signs strong indicators of disease present? (For example, diseases that cause sudden death or diseases with obvious signs will be detected faster.)	6.00%	6.14%
Mitigation Measures		
13. Are effective diagnostic tests available in the country for humans?	5.40%	0.00%
14. Are effective post exposure treatments (including immuno-globulin, vaccines and anti-microbials) available in the country for humans?	9.20%	0.00%
15. Are preventative measures (vaccines) available in the country for humans?	5.40%	0.00%

Question	Human Consequences Weight	Animal Consequences Weight
16. Are effective diagnostic tests available in the country for animals?	0.00%	5.20%
17. Are effective post exposure treatments (including immuno-globulin, vaccines and anti-microbials) available in the country for animals?	0.00%	9.00%
18. Are preventative measures (vaccines) available in the country for animals?	0.00%	5.20%
19. Are secondary consequence measures feasible in the country for animal populations?	0.00%	0.60%
<u>Secondary Transmission</u>		
<u>Transmission</u>		
20. How easily does this agent transmit between human hosts?	6.89%	6.89%
21. How easily does this agent transmit from animal to human hosts?	2.86%	2.86%
22. How easily does this agent transmit from human to animal hosts?	0.71%	0.71%
23. How easily does this agent transmit between animal hosts?	1.55%	1.55%
<u>Routes</u>		
24. 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?	1.20%	1.17%
25. 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?	0.15%	0.15%
26. Is this agent known to cause infection via direct contact (to cause infection through the mucosal membranes) in the natural environment?	0.75%	0.66%
27. Is this agent known to cause infection via ingestion (to cause infection via contact with the gastrointestinal tract) in the natural environment?	0.51%	0.51%
28. 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))?	0.24%	0.24%
29. 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)?	0.09%	0.09%
30. Is this agent known to cause infection via sexual transmission (to cause infection through sexual contact including intercourse)?	0.18%	0.18%

B.2. Security Systems Effectiveness Questions

Question	Insider Weights	Outsider Weights
Security Culture		
1. Does the institution have defined roles and responsibilities for biosecurity?	5.40%	4.32%
2. Has the institution made a commitment to security?	7.80%	6.24%
3. Does the institution have comprehensive biosecurity documentation?	2.00%	1.60%
4. Does the institution conduct biosecurity drills or exercises?	2.00%	1.60%
5. Does the institution periodically review the biosecurity program?	2.80%	2.24%
Physical security		
1. What type (if any) of a perimeter security exists outside the building(s)?	0.00%	3.00%
2. How many barriers exist between public areas and the biological agent?	0.00%	7.20%
3. Does the building housing the select biological agent or toxin limit access through a control system when the building is not occupied?	0.00%	10.80%
4. Does the room housing the select biological agent or toxin limit access through a control system when the room is not occupied?	3.00%	10.80%
5. Do the select biological agents or toxins storage areas (freezers, culture collection, etc.) limit access through a control system?	1.60%	6.00%
6. Are ALL individuals with access to the room, work areas, and any storage areas where select biological agents and toxins exist specifically approved for access?	1.20%	4.20%
7. Do intrusion detection systems exist in the areas where select biological agent or toxins are used or stored?	1.50%	5.40%
8. Are ALL doors (or other potential entry points) covered by an intrusion detection system?	1.50%	5.40%
9. How are alarms assessed?	0.60%	3.60%
10. How are alarms responded to?	0.60%	3.60%
Personnel Reliability		
1. How are personnel vetted prior to allowing them unescorted access to the agent?	13.50%	0.00%
2. How are the personnel vetted who will not have direct access of the agent?	4.50%	0.00%
3. How are visitors and other individuals who have not been vetted escorted when accessing rooms with the biological agent or other materials?	6.75%	0.00%
4. Are badges worn?	2.25%	8.00%
5. Do badges indicate level of access allowed by the wearer?	2.25%	0.00%

Question	Insider Weights	Outsider Weights
6. Does badge include a photo of the wearer (owner) and a time interval for when it is valid?	3.60%	0.00%
7. Are there procedures for returning badges or reporting lost badges?	3.60%	0.00%
8. What is the level of biosecurity training provided?	6.75%	0.00%
9. Do employee assistance programs exist?	1.80%	0.00%
Transport Security		
1. What is the level of control at a facility of materials moving between laboratories or while in shipping/receiving areas?	1.50%	0.00%
2. What type of vetting is required for personnel transporting material within the facility?	2.00%	0.00%
3. What type of administrative approvals is required for internal transport?	0.70%	0.00%
4. What type of administrative approvals is required for external transport?	1.40%	2.50%
5. What is the required security level for the receiving facility when sharing this agent?	1.60%	2.80%
6. How are agents packaged for external transport?	1.20%	2.10%
7. How are external carriers selected?	1.50%	2.60%
Material Control and Accountability		
1. How does the facility determine which materials are subject to material control and accountability (MC&A) measures?	2.00%	0.80%
2. Which materials are inventoried?	1.50%	0.60%
3. What is the level of control of agents while in use (working stocks, infected animals, etc.)?	3.50%	1.40%
4. Are there clearly defined accountability roles and responsibilities?	1.00%	0.40%
5. Are there clearly defined procedures for material control and accountability (MC&A)?	2.00%	0.80%
Information Security		
1. Has information which is considered sensitive been clearly identified, marked, and protected at a level equivalent to the risk of loss or release?	0.85%	0.34%
2. Is information which is considered sensitive protected from release or loss?	1.40%	0.54%
3. Are there clearly defined communication policies regarding sensitive information?	0.50%	0.20%
4. Are electronic critical infrastructure systems (including inventory databases, alarm control stations, access control systems, building monitoring systems, etc.) protected from attack?	1.05%	0.40%
5. Are there clearly defined policies for public disclosure of information?	0.80%	0.32%

Question	Insider Weights	Outsider Weights
6. Are electronic physical security systems (alarm control stations, access control systems, building monitoring systems, etc.) isolated from the public internet?	0.50%	0.20%

APPENDIX C. APPENDIX JAVA VERSION SOFTWARE DIRECTIONS

The following are the general direction for using the java version of the BioRAM software tool reflecting the files names located in the GitHub repository.

4.1.1. Java Version - Files

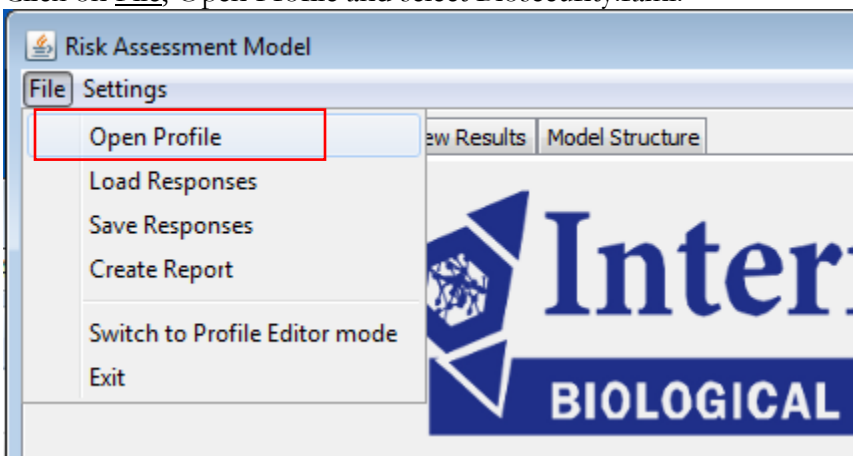
To run the BioRAM tool, you will need the bioram-4.0.5.exe file (or bioram-4.0.5.jar) and the BiosecurityRAM.raml. The tool will require Java installed on your system.

The BiosecurityRAM.raml tool is in English, but there are versions in Spanish, Russian, Indonesian, and French also available on the GitHub repository. These have the same name but include a two-digit code reflecting the language (fr for French, es for Spanish, ru for Russian, and id for Indonesian)

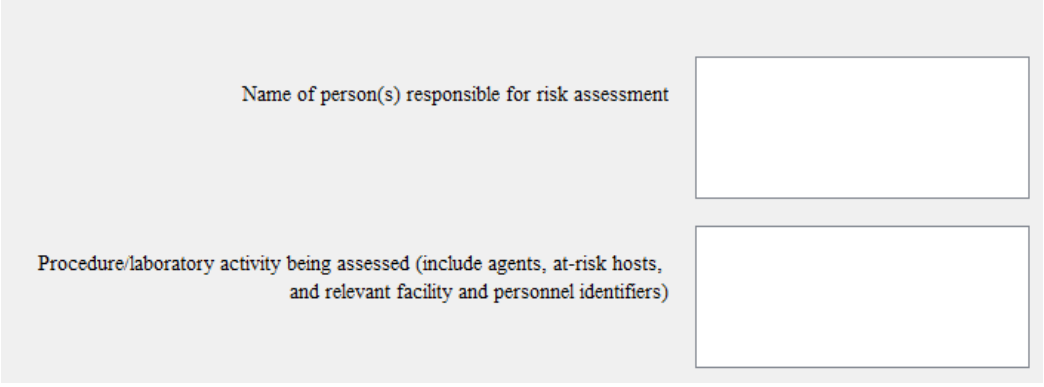
These files need to be in the same folder located on your local computer. This tool does not connect to or store files outside your local computer unless you set it to do so.

4.1.2. Java Version - Running BioRAM

Start the BioRAM-4.5.1.exe file, this will open a grey window with no information in any of the tabs. Click on File, Open Profile and select Biosecurity.raml.



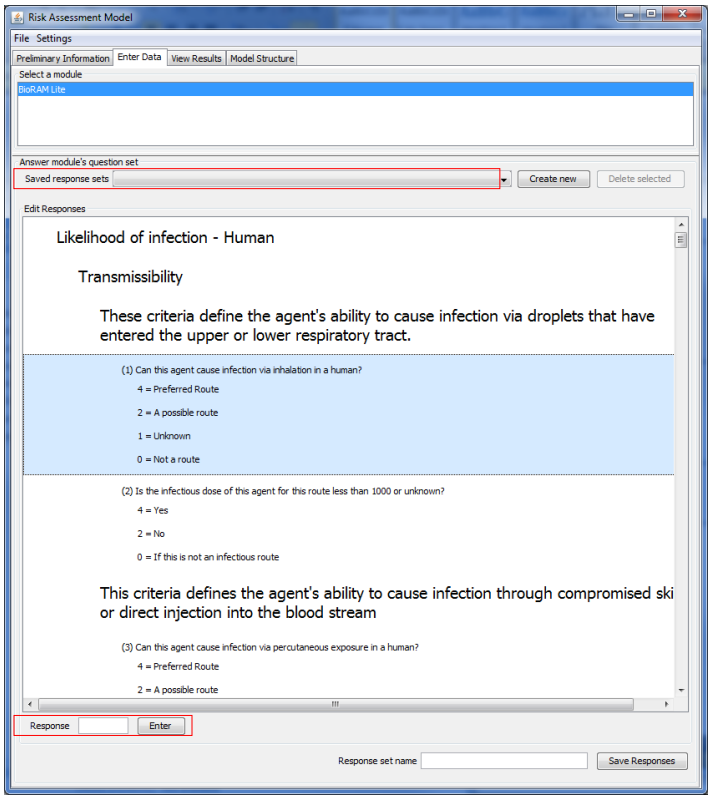
On the Preliminary Information tab, enter details to ensure proper documentation will accompany your results



4.1.3. Java Version - Creating an Assessment

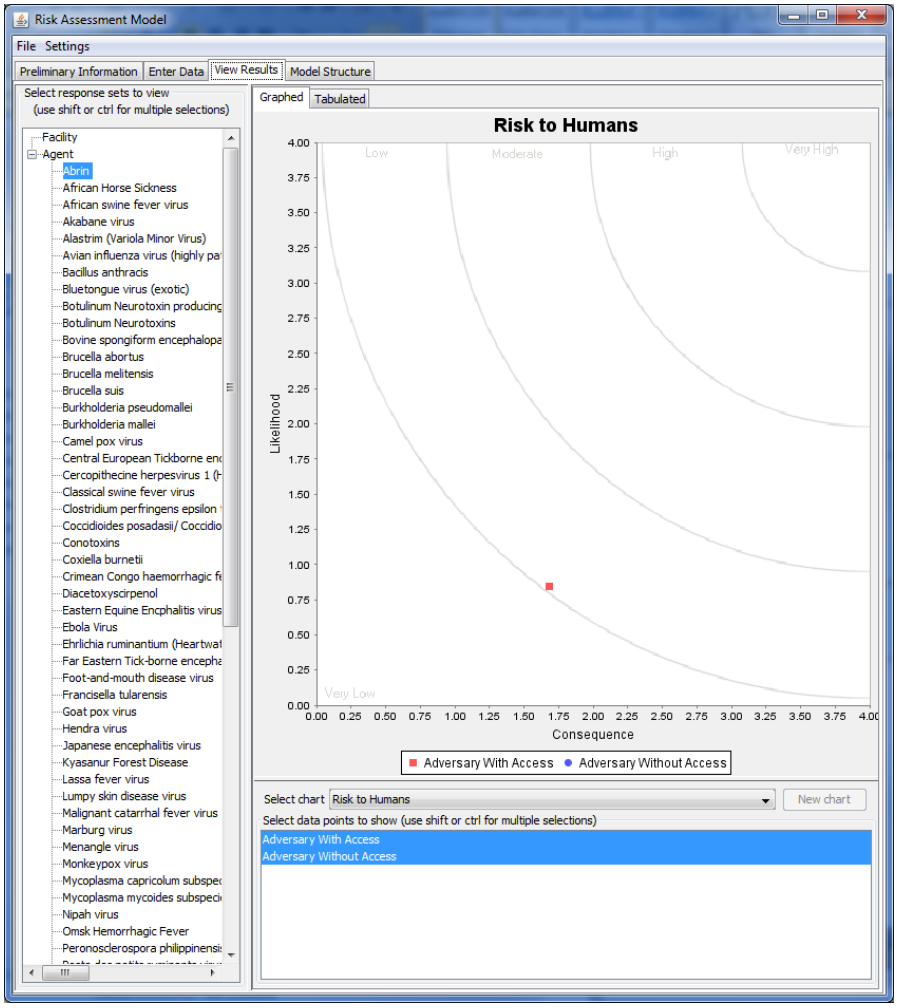
Select the Enter Data Tab and select from one of two modules which divide the overall assessment into two sections, Facility or Agent sections. Fill out each questionnaire by selecting each question and answering in the response field at the bottom (1). Once both modules are complete, name and save your responses. These can be accessed later if needed (2). A selection of biological materials has been defined under the agent selection, these can be altered or added to as needed to reflect your facility. These were defined conducting a literature review of biological materials outside of the BioRAM effort.

2

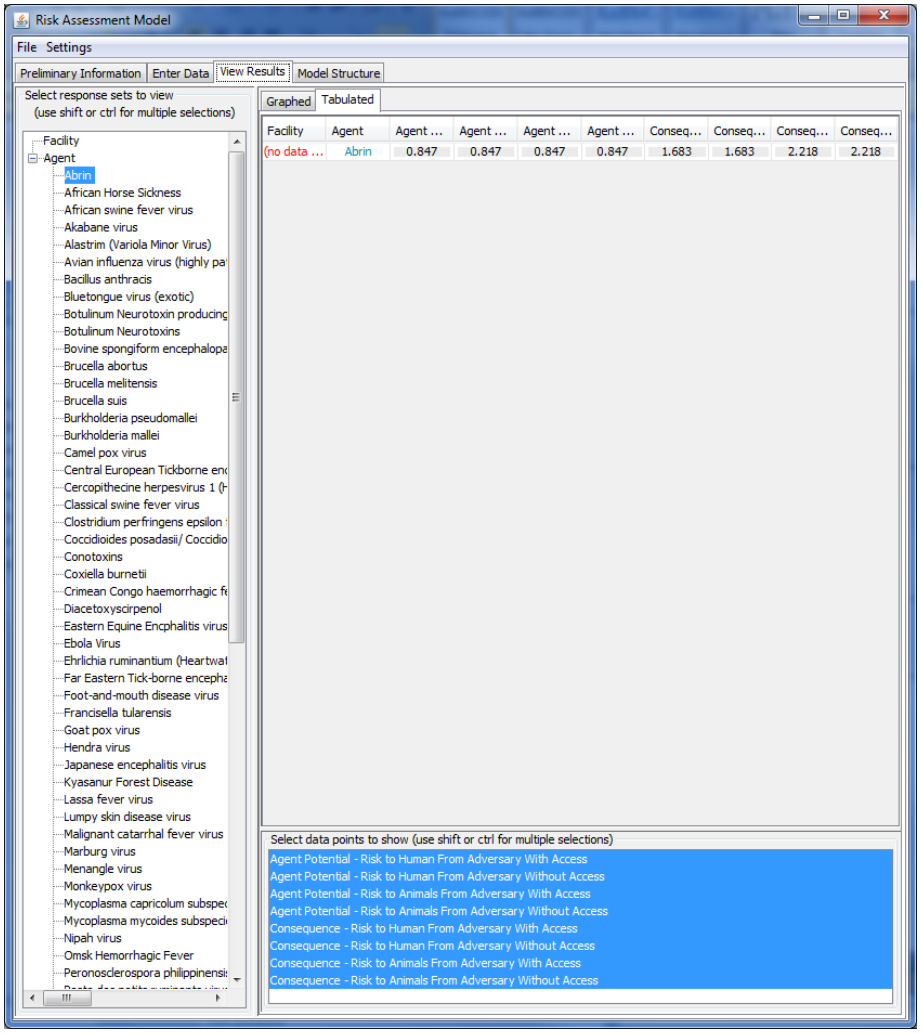


1

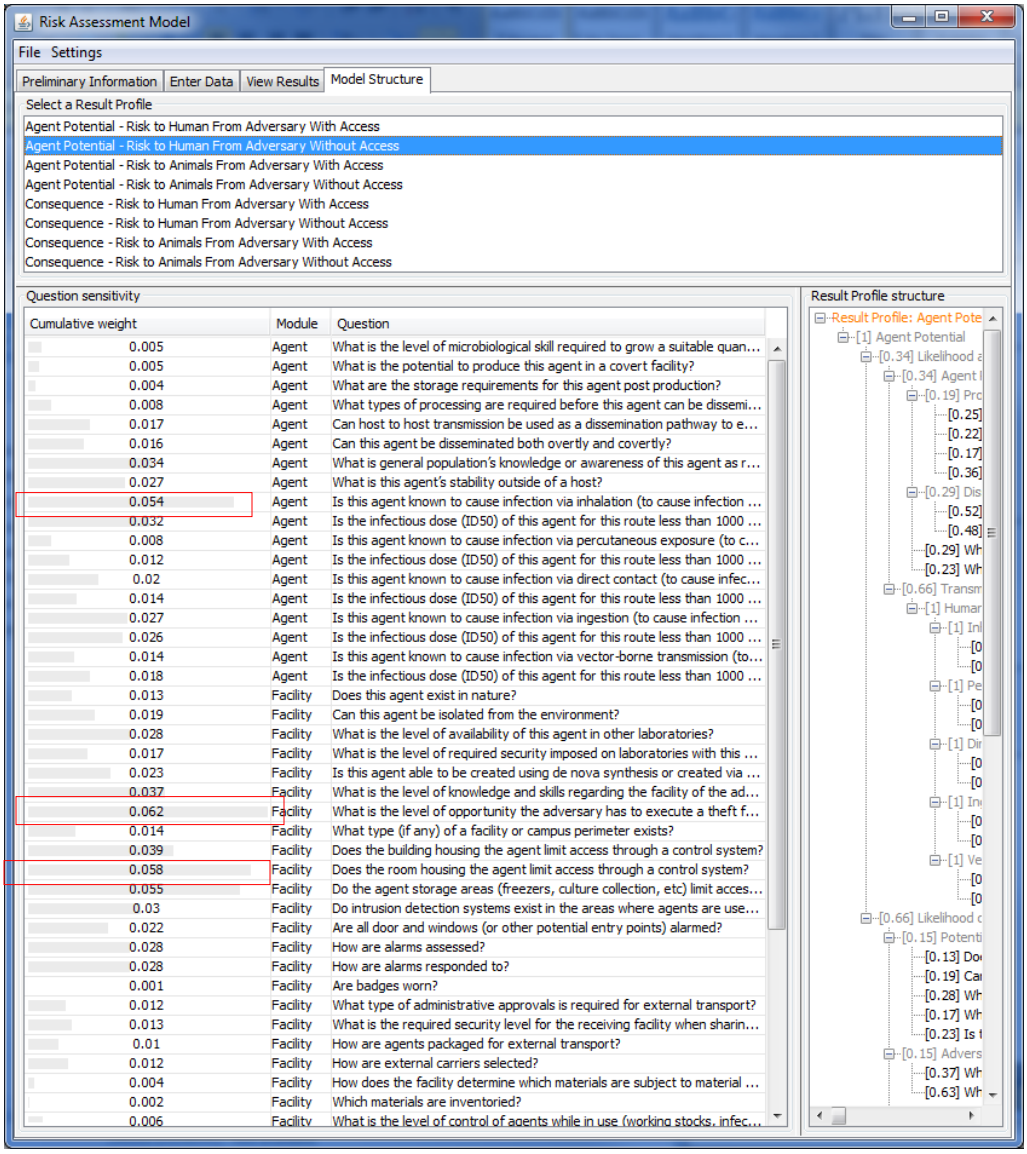
Under the view Results tab select the agents and facilities, you would like to view, you can select multiple agents and a single facility to reflect multiple agent's relative risk within the same laboratory or select multiple facilities to relatively compare different laboratories. You can select human or animal risks and limit the assessment to just those with or those without access.



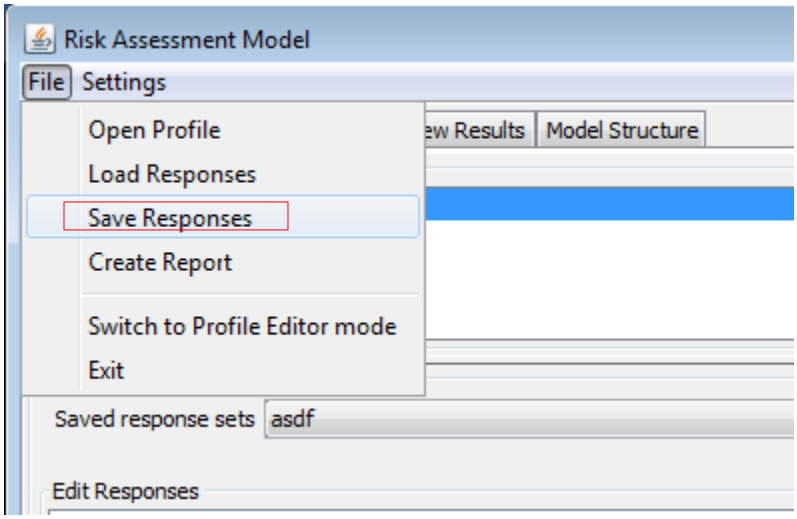
The tabulated sub-tab will give you numerical answers, which can be useful in exporting to other programs



The Model Structure tab allows you to see the risk drivers, looking at the question sensitivity chart will help to define the biggest drivers.



Under File, save your responses (Save Responses). This will allow you to load them later (Load Reponses).



You can also create a report (Create Report) to export the results into a printable format.

5. REFERENCES

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