Review of Risk Assessment Work Plan for the Medical Countermeasures Test and Evaluation Facility at Fort Detrick: A Letter Report

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Committee on Risk Assessment of the Medical Countermeasures Test and Evaluation (MCMT&E) Facility at Fort Detrick, Maryland; National Research Council

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A Letter Report

Committee on Risk Assessment for the Medical Countermeasures Test and Evaluation (MCMT&E) Facility at Fort Detrick, Maryland

Board on Life Sciences

Division on Earth and Life Studies

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500 Fifth Street, NW
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September 16, 2011

Major General James K. Gilman
Commander
U.S. Army Medical Research and Materiel Command
504 Scott Street
Fort Detrick, MD 21702-5012

Dear Major General Gilman:

At the U.S. Army's request (pursuant to Contract No. W81K04-06-D-0023 [CLIN 3005]), the National Research Council (NRC) established the Committee to Review Risk Assessment Approaches for the Medical Countermeasures Test and Evaluation (MCMT&E) facility at Fort Detrick, in Frederick, Maryland. The committee was charged with reviewing a proposed approach to preparing a risk assessment for the new biocontainment laboratory at the base. Enclosed is the committee's second letter report on the Army contractor's proposed work plan for conducting the risk assessment.

Sincerely,

Charles N. Haas, Ph.D.
Chair, Committee to Review Risk Assessment Approaches for the Medical Countermeasures Test and Evaluation Facility at Fort Detrick, Maryland

INTRODUCTION

This letter report reviews a work plan for conducting a site-specific risk assessment (SSRA) for the Army's Medical Countermeasures Test and Evaluation (MCMT&E) facility at Fort Detrick in Frederick, Maryland. The development of the work plan was informed by findings and recommendations made by this committee (see Attachment A for roster and biographies) in a letter report issued in May 2011, who commented on proposed approaches for conducting the SSRA (NRC 2011a). The following background on the request for these reviews is excerpted from the committee's first letter report.

The U.S. Army Medical Research and Materiel Command (USAMRMC) plans to construct and operate a new Medical Countermeasures Test and Evaluation (MCMT&E) facility at Fort Detrick in Frederick, Maryland. The proposed site of the 492,000-square-foot facility is on the north side of the fort's National Interagency Biodefense Campus.[1] The facility will be designed to handle infectious agents that are considered Category A and Category B under the Centers for Disease Control and Prevention schedules and that require safety precautions to the extent of animal biosafety level-3 (ABSL-3) and ABSL-4 and biosafety level-3 (BSL-3) and BSL-4. Researchers at the facility will develop new vaccines and drugs against such pathogens as *Ebola* virus and *Bacillus anthracis*. The laboratories will be equipped to support nonhuman primate studies and have modern aerobiology and telemetry (remote monitoring) capabilities. Research with rodents will also be conducted.

An environmental impact statement (EIS) is currently being developed by an Army contractor for the MCMT&E facility. EISs are documents required under the National Environmental Policy Act (NEPA) of 1969 to identify and characterize the probable environmental impacts from programs and actions of the federal government. Human health effects are one of the many impacts considered in EISs. Agencies with biocontainment laboratories have struggled with approaches to conducting human health risk assessments, particularly because there is no generalizable framework that can be applied to assessing the specific risks from such laboratories. Recent reviews conducted by the National Research Council (NRC) of risk assessments performed to support the construction of biocontainment facilities have identified weaknesses in both the process and technical content of the assessments by other agencies and provide guidance for improvements (NRC 2007, 2008, 2010a,b,c,d).

In 2010, an NRC committee evaluated the health and safety risks of another Fort Detrick facility with high-containment laboratories—the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). The evaluation included a review of a health hazard assessment for the new USAMRIID laboratories, as well as procedures and regulations for their operation. The committee found that the hazard assessment failed to provide adequate and credible technical analyses of the potential health risks to the general public. The Army was advised to improve its risk-assessment practices for infectious agents in future EIS processes and products (NRC 2010a). Thus, to support the EIS being developed for the new MCMT&E facility, the Army requested a review of its site-specific risk-assessment (SSRA) plans for the MCMT&E facility.

CHARGE TO THE COMMITTEE AND ITS APPROACH

The committee was tasked with reviewing and providing technical input to a new environmental impact statement (EIS) to be prepared for the Medical Countermeasures Test and Evaluation (MCMT&E)

[1] Other facilities that comprise the National Interagency Biodefense Campus include the U.S. Army Medical Research Institute of Infectious Diseases, the Department of Homeland Security's National Biodefense Analysis and Countermeasures Center, and the National Institute of Allergy and Infectious Diseases' Integrated Research Facility.

facility. This facility is intended to be built and operated on area A of Fort Detrick. Technical input may include, but may not be limited to, a proposed work plan for preparing risk assessments as well as information on the selection of agents, scenarios, and models to be used in the risk assessments. The committee may also be asked to review preliminary model results for the quantitative risk assessments and any qualitative assessments developed where data may be insufficient for quantitative modeling. The committee will not perform an independent evaluation of the safety of the MCMT&E facility or the EIS as a whole, but will restrict its findings to assessing the adequacy and validity of the proposed risk assessment methodology and the draft results of any assessment to be incorporated into the EIS.

The Army originally expected that the committee would review a completed SSRA as its second and final task. However, on the basis of the recommendations of the committee's first report, the Army decided to have the committee review a formal work plan for the SSRA so that the Army could obtain further guidance before the SSRA is performed. The committee held two meetings to address this task. One meeting was held on May 18, 2011, to obtain input from members of the Containment Laboratory Community Advisory Committee[2] and the general public. Another meeting was held on July 25-26, 2011, at which the Army's contractor BSA Environmental Services, Inc., presented a work plan for conducting an SSRA for the MCMT&E facility (see Attachment B). The findings and recommendations in this letter report reflect the consensus of the committee, and the report was reviewed in accordance with standard NRC review procedures (see Attachment C). Some aspects of the work plan were vague; for example, the methods for conducting certain types of analyses were not specified. Because of this, some of our recommendations are framed broadly. In these cases, we have tried to provide citations to relevant references to case studies, guidance documents for certain analytic approaches, and other NRC reports that have evaluated similar types of risk assessments.

OVERARCHING FINDINGS

The committee first compliments BSA Environmental Services, Inc., and its team for considering elements from the first letter report (NRC 2011a) in the development of its work plan. The work plan provides a better overall description of the scope and plans for conducting the risk assessment than that of the previous plan. In particular, the work plan includes helpful illustrations of what exposure pathways will be considered in the risk assessment for specific agents and outlines steps for performing qualitative and quantitative analyses.

The purpose of any risk assessment is to help inform decision makers and stakeholders about the consequences of a particular set of decisions and scenarios. "Risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk rather than as an end in itself" (NRC 2009, p. 5). However, the objective stated in the submitted work plan is "to document the likelihood, adverse consequences, and uncertainty of reasonably foreseeable events that can affect the health of people working in and around the laboratory as well as members of the community" (BSA Environmental Services, Inc., 2011, p. 1). The committee believes that an assessment should be viewed not merely as a regulatory hurdle to be overcome but also as a tool to be used to enable the most desirable alternative or policy to be implemented. In this regard, the separation of the risk assessment from facility design reduces the overall usefulness of the assessment to decision making. In the absence of one or more actual alternatives for a facility, it should not be assumed that any SSRA would have validity under all alternatives that might be considered in an environmental impact statement.

The work plan focuses on the direct consequences of a release event from the proposed laboratory. Heavy reliance is placed on examination of retrospective reports of laboratory-acquired

[2]The Containment Laboratory Community Advisory Committee was formed by the Frederick Board of County Commissioners and the City of Frederick to foster communication between the public and operators of containment laboratories at Fort Detrick and elsewhere in Frederick, Maryland.

infections (LAIs). There are limitations to this approach (Singh 2009). Looking retrospectively at historical events is important but cannot assess events that are of low likelihood (but possibly of higher consequence) that have not (yet) been observed. A robust risk assessment should proactively assess the likelihood and consequence of potential events. A variety of tools are available to do that, and some are discussed in detail below. It also would be prudent to consider to the extent possible the potential indirect consequences of a release.

The committee finds that the methodology of the SSRA is not sufficiently robust to assist the Army in designing a facility that will reduce the risk from potential hazards from the facility's operations. By improving its approach, the Army can ensure the value, timeliness, and credibility of the risk assessment and develop a facility that will protect human health, the environment, and cultivate public confidence.

SCOPING AND PROBLEM FORMULATION

Agents under Consideration

The SSRA work plan proposes to review six agents or groups of agents:

- *Bacillus anthracis*
- *Brucella* spp.
- Ebola and Marburg viruses (viral hemorrhagic fevers)
- *Francisella tularensis*
- Venezuelan, eastern, and western equine encephalitis viruses
- *Yersinia pestis*

The committee was told that there are current plans for research on these agents at the proposed facility. The agents may not, by definition, be considered a representative list of all pathogens that may ultimately be investigated at the facility. Furthermore, the work plan did not address the committee's previous recommendation that countermeasures also be included in the SSRA (e.g., vaccinia-based vaccines, antibacterial or antiviral drugs). For this reason, the first letter report questioned the decision to exclude dry-use scenarios (NRC 2011a). We continue to question this exclusion in the work plan when vaccinia virus will be used as a vector for vaccine delivery. Some vaccines are manufactured in lyophilized or freeze-dried formulations (e.g., Kastenmuller et al. 2009), and countermeasure testing would include evaluating the efficacy of such formulations. See Communication section below for discussion of the importance of clarifying who will be responsible for conducting and approving risk assessments of other agents when they are added to the research portfolio.

Range of Validity Because Facility Has Not Been Designed

In the first letter report, this committee stated that "a sufficiently detailed understanding and characterization of the design and engineering controls of the facility are needed to perform the SSRA adequately. In this case, because the facility has not yet been designed, it may be premature to scope the SSRA fully. It is conceivable for the scoping to be done in parallel with the design of the facility; however, the relative time lines for these two processes were not clear from the briefing" (NRC 2011a).

It remains the case that the facility has not yet been through the conventional infrastructure design phase, yet the SSRA is moving ahead. Therefore, the SSRA needs to be fully transparent about the assumptions being made in regard to facility design (especially in light of possible changes in size and scope [Eckstein 2011]), construction, and operation. The scope should incorporate the key elements and

assumptions with respect to the facility design and associated value engineering that may influence risk to workers and offsite populations. Substantial differences in design that have the potential to increase risk may require a supplemental risk assessment.

End Points Considered

The previous letter report recommended a clear delineation of the metrics or end points that will be used for risk characterization in the SSRA. The work plan describes all scenarios as having one or more end points, which are no adverse effect, illness, and mortality. These end points are considered direct consequences from a particular scenario (e.g., accidental exposure in a laboratory); however, other indirect consequences may occur as a result of an adverse event, which include economic, social, and healthcare impacts. For example, the 2001 anthrax letter attacks had the direct impact of killing five people and infecting 17 others. However, the indirect impact was that over 30,000 people received prophylactic treatment and many buildings were decontaminated, all at a cost of over $1 billion (CDC 2001; NRC 2011b). Other SSRAs of proposed biocontainment facilities have assessed indirect consequences of an adverse event. For example, the Department of Homeland Security estimated that the economic impact of an outbreak of disease from a laboratory release of the foot-and-mouth-disease virus from the National Bio- and Agro-Defense Facility, if it were to be located in Manhattan, Kansas, could be $9-$50 billion. The NRC committee that reviewed that SSRA estimated that the risks and costs could be even larger (NRC 2010c). These examples highlight the importance of incorporating other metrics when doing consequence analysis. Therefore, the committee recommends estimating the potential indirect and direct impacts for all scenarios to the extent possible.

Assessment of Evidence

The work plan does not adequately address the previous letter report's recommendations for assessing risks from LAIs. Specifically, the work plan fails to consider the full range of potential occupational exposures. The Centers for Disease Control and Prevention (CDC) reports 395 cases of potential release events at national laboratories working with select agents (see Table 1). Seven LAIs were reported to CDC; four infections involved *Brucella melitensis*, two involved *Francisella tularensis*, and one involved an unspecified *Coccidioides* species (NRC 2011c). CDC plans to publish an analysis of these events.

TABLE 1 Activity Resulting in Potential Release of Select Agents, 2003-2009

Activity	No. Potential Release Events
Animal bite or scratch	11
Needlestick or sharps injury	46
Equipment mechanical failure	23
Personal protective equipment failure	12
Loss of containment	196
Procedural issue	30
Spill	77
Total release events	395

SOURCE: CDC, unpublished material, Nov. 2010, as cited by NRC (2011c).

The accidental release data show the potential for exposure by accident to occur. Fort Detrick has kept records and published peer-reviewed papers on LAIs (e.g., Rusnak et al. 2004a, b, c). These and other detailed incident reports should be evaluated to determine failure modes and rates, which can inform

a formal failure analysis for assessment of exposure likelihoods and frequencies in a formal risk assessment. Failure analysis involves the systematic evaluation of engineering, procedural, and process failures that could lead to the release of a pathogen from the laboratory.

The work plan addresses infections among laboratory workers and their primary contacts. Data on LAIs in administrative, maintenance, and waste-handling staff, for example, should also be analyzed. Example references include Meyer and Eddie (1941) and Fiori et al. (2000).

Exposures have the potential to occur outside the laboratory. Therefore, failure-mode analysis should be conducted on agent transport, biohazard waste transport, treatment, storage, and disposal, recognizing the scale of work contemplated at the facility and the differences in infrastructure design, the changes made during the value-engineering phases, and the final facility "as built" and operated. The committee recognizes that failure analysis itself is imperfect; however, it is perhaps most useful in assessing the relative importance of design and operational decisions to performance and is preferable to ad hoc empirical judgments (Seife 2003).

Data Quality Standards for Literature Used

A retrospective historical analysis forms the basis of much of the proposed risk assessment approach. The systematic review required to undertake such an approach is extensive (Higgins and Green 2011). The work plan should include procedures for obtaining data and information and criteria for selecting data for inclusion. For example, the preamble to the White House Office of Management and Budget (OMB) Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies states that

> 'agencies shall have a basic standard of quality (including objectivity, utility, and integrity) as a performance goal'…. [OMB] note[s], in the scientific context, that in 1996 the Congress, for health decisions under the Safe Drinking Water Act, has already adopted a basic standard of quality for the use of science in agency decisionmaking. Under 42 U.S.C. 300g-1(b)(3)(A), an agency is directed, 'to the degree that an Agency action is based on science,' to use '(i) the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data).' [OMB] also note[s] that the OMB guidelines call for an additional level of quality 'in those situations involving influential scientific or statistical information.' The additional level of quality concerns a standard of care for scientific or statistical analytical results, a 'capable of being a substantially reproduced' standard… (OMB 2001).

In this way, the risk assessment reports can be further scrutinized for data quality, bias, and assumptions. Of the 22 references cited in the work plan, eight were not peer-reviewed and three were not appropriately referenced (e.g., symposium reports, institutional reports, professional society newsletters, and Web sites). Recognizing that this document is the work plan, the committee urges the SSRA to be more scrupulously researched and documented.

Definition and Boundaries of the Problem Scope

More precision is needed in defining the terms *plausible*, *likely*, and *reasonably foreseeable*. A clear statement is also needed on the boundaries of the scope of the problem, which hinges on how the three terms are defined. In the text of the work plan, the terms *implausible* and *unlikely* were used synonymously; therefore, an event deemed unlikely would not be further evaluated.

The term implausibility is a descriptor based on existing knowledge of biological and physical processes as well as design features of the laboratory. The term unlikely is a metric based on a probability (unlikely adverse events have a low probability of occurring). Consistent with the work plan, it is a reasonable decision to not explore implausible routes of transmission; however, unlikely risk scenarios should not be excluded from the assessment. The work plan describes an unlikely event as one that has no historical data that it occurred; however, not all events that have not yet been experienced are unlikely. Unlikely events are not impossible, and it is the unprecedented event that often has resulted in severe outcomes.

On the basis of a more explicit definition of likelihood and plausibility, the work plan also should contain a more precise definition of a *reasonably foreseeable scenario*. A statement of how these scenarios will be developed would provide more clarity on the scope of the risk assessment. For example, these scenarios could be developed in a way that provides the framework for a formal failure analysis, an analysis that the committee recommended as a major component of the risk assessment (NRC 2011a). The committee's view on the need to include failure analysis in the risk assessment is discussed further below.

Scenarios (Pathogen Maps)

The committee appreciates the convenience and creativity of the "pathogen maps," adapted from NRC (2009), provided within the work plan (for *F. tularensis*) and as appendixes for the other five organisms or class of organisms. The end point of all risk assessments in this project are human infections, and the utility of these maps is that they provide an overview of all possible routes of infection, from the initial event (accidental exposures in the laboratory and accidental or intentional releases from the laboratory) to the final possible end points (no adverse effect, illness, or mortality). The approach taken in the work plan appears to be that if a pathway of exposure has been documented in the past, it is analyzed as an exposure pathway; pathways that have not been documented are excluded. The committee recommends the opposite approach of assuming that all pathways are potential routes of exposures and then assessing whether there is justification and affirmative documentation to rule that linkages to the potential routes are implausible and then to remove them. Specifically, an exposure pathway may be excluded because of a lack of information that a causal linkage is plausible or because sufficient information exists that a linkage is implausible. The decision process for construction of these maps should be fully documented with appropriate references. Producing a final map in this way will ensure that due diligence was used to analyze routes of infection or release.

The maps also should include all plausible sources and routes of exposure. For example,

1. Waste streams from laboratory and animal studies.
2. Accidental contamination of the ecosystem resulting in formation of a reservoir for infection (e.g., soil and water).
3. Wild animals/insects entering the facility and coming into contact with agents and waste products. For example feral rodent penetration may explain outbreaks of hantavirus in animal colonies in Belgium (Desmyter et al. 1983), France (Dournon et al. 1984), Japan (Umenai et al. 1979; Kawamata et al. 1987), the United Kingdom (Lloyd et al. 1984; Lloyd and Jones 1986), and Singapore (Wong et al. 1988).

DECIDING ON ANALYSIS APPROACH (QUALITATIVE/QUANTITATIVE DECISION MAKING)

The work plan lays out a two-tier process of conducting a risk assessment for scenarios, indicating that an initial qualitative risk assessment may be followed by a quantitative assessment. The work plan does not adequately describe the criteria that will be used to decide whether a quantitative assessment will be performed. In general, quantitative risk assessment is the preferable approach even in the presence of large data gaps:

> Many factors may influence the decision to conduct a qualitative versus a quantitative risk assessment. Obviously, if no data are available to make inferences from, then a quantitative risk assessment would not be possible. Constraints in data quality, time, personnel, or resources may not permit a full quantitative risk assessment. *However, data gaps are not necessarily a barrier to quantitative risk assessment.* Our bias has been towards 'Letting the data speak!', using thorough data analysis, formal inferencing, and striving for complete documentation of variability and uncertainty" (Coleman and Marks 1999, p. 290, emphasis added)

The decision not to perform a quantitative assessment should be explicitly justified in every case. Specifically, rigorous metrics based on peer-reviewed information should be formalized when deciding the appropriate approach. Decisions with respect to deliberately induced events could be informed by risk assessment approaches developed for such incidents. Several approaches used by the Department of Homeland Security were recently reviewed by the NRC (2010e), including the Terrorism Risk Assessment and Management risk assessment (a software-based tool for performing terrorism-related relative risk analysis). Although the NRC report concluded that the model remains to be validated, it found the approach provides a structured process for conceptualizing and ranking the spectrum of risks.

CONDUCT OF THE QUALITATIVE RISK ASSESSMENT

The approach to the qualitative risk assessment in the work plan is not described in sufficient detail to be evaluated by a practitioner versed in risk assessment. The relevance of Figure 2 in the work plan to qualitative risk assessment is unclear. It does not appear that standard qualitative risk assessment approaches will be used. For example, a two-dimensional outcome matrix consisting of likelihood of hazard and magnitude of consequence is a common approach (Cox et al. 2005).

If this methodology is used, the following questions apply:

- How many categories in each dimension will be used?
- What are the criteria for assigning a likelihood value and a consequence value to a scenario?
- How will the output of this qualitative assessment be used?

The work plan should include clear statements on the precise format and techniques of a qualitative risk assessment, as well as its goals and outcomes.

CONDUCT OF THE QUANTITATIVE RISK ASSESSMENT

The goals of a quantitative risk assessment are to determine with specificity the extent and magnitude of adverse consequences associated with a policy option, scenario or decision. This

determination may be done as a point estimate or with the use of probabilistic (Burmaster and Anderson 1994), interval (Ferson and Ginzburg 1996), or other methods to determine the uncertainty of such estimates. The value of quantitative risk assessment is determined by the quality of the uncertainty analysis. Uncertainty estimation helps to ascertain which inputs are the most significant sources of uncertainty; these sources would be key targets for further data-gathering efforts.

The work plan introduces the terms "coarse grain" and "fine grain" in the discussion of quantitative risk assessment. These terms are unnecessarily confusing. There are tiered approaches of sophistication to the execution of a risk assessment, particularly with respect to uncertainty and variability analyses (see NRC 2009, 2010e), and alternative approaches have been reviewed (Paté-Cornell 1996). Figure 1 shows the spectrum of traditional risk analysis methods. The SSRA work plan should adopt more conventional risk assessment terms and should also indicate the criteria by which higher tiers of analyses might be used. For example, a lower-tier analysis (e.g, a point estimate or an exposure estimate based on lumped parameter models) that indicates the existence of a risk might justify a higher-tier analysis (e.g., one- or two-dimensional Monte Carlo analysis or spatial discretized transport models), which could identify the key variables that dominate the uncertainty in the risk estimate.

The use of quantitative risk assessment requires inputs on exposure and dose response. In the context of the MCMT&E facility, because the building is not yet designed, the most appropriate method to estimate exposure extents and likelihoods (which would be needed as inputs to quantitative risk assessment) would be failure analysis. Failure analysis is used in a number of settings in which complex facilities, such as chemical-process, nuclear-power, and space industries, are analyzed (Garrick 1988; Apostolakis and Kafka 1992; Kumamoto and Henley 1996). The committee believes that this method would be eminently appropriate for the MCMT&E facility. One advantage of using failure analysis is that information on other facilities that have common equipment or failure modes (e.g., failure of a waste backflow valve) could be used to inform the process.

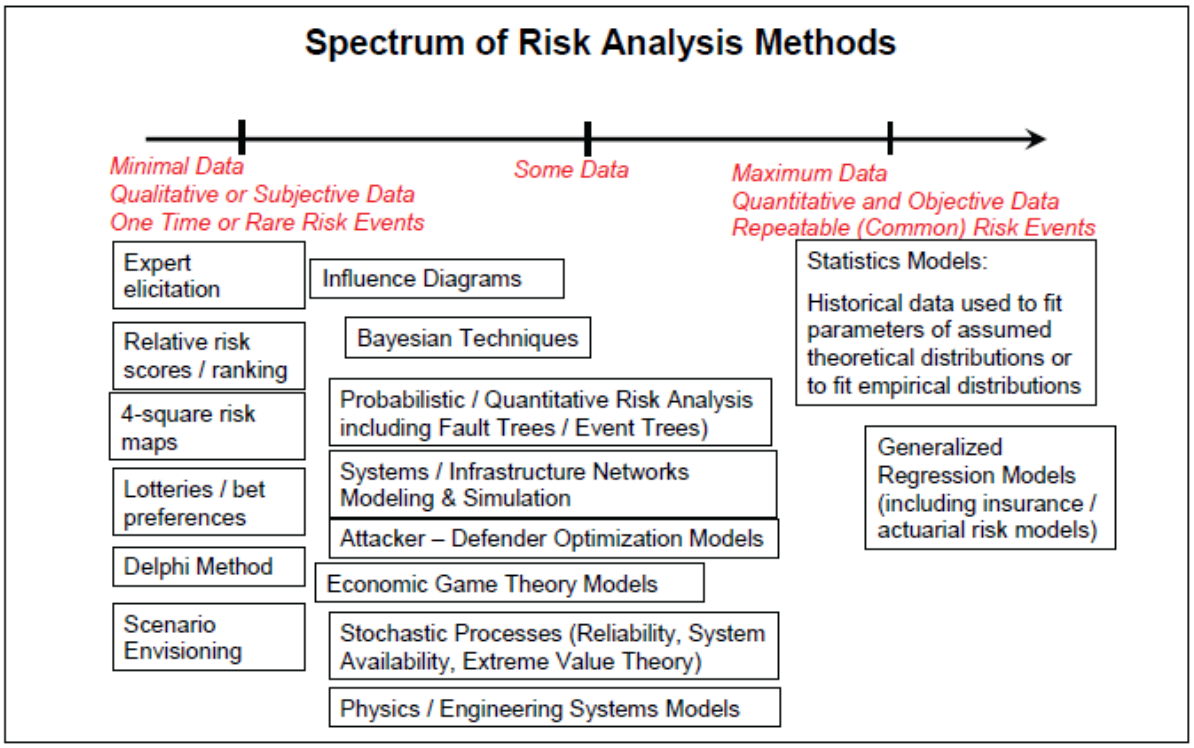

FIGURE 1 Spectrum of risk analysis methods. Source: NRC 2010e.

In the event that dose-response information for a particular pathogen of interest is not available, there are several approaches that can be used. While recognizing the limitations, one common approach is to use an organism that is considered to have similar characteristics; for example, when *Escherichia coli* O157:H7 rose to concern in food and water, the dose-response relationship for *Shigella* was used as a proxy (due to O157:H7 having common pathogenicity characteristics) (Duffy et al. 2006). Another approach is to use as an extreme the limiting upper bound of an exponential dose-response curve that has an individual organism survival probability of 1 as the upper possible limit (Teunis and Havelaar 2000).

COMMUNICATION

There is a great deal of concern among local residents that releases of biological agents (e.g., agents classified by CDC as Category A) from the research programs at Fort Detrick may lead to disease outbreaks in the surrounding community. Therefore, the committee compliments BSA Environmental Services, Inc., for its plans to devote a large amount of effort to address community concerns through risk communications. As stated in the previous letter report, the committee again acknowledges the Army's cooperation with the Containment Laboratory Community Advisory Committee (CLCAC). Members of the committee who met with representatives of the CLCAC have seen how direct, informal interchange improves public understanding of the work of Fort Detrick's biocontainment laboratories (information on the activities of the CLCAC is available at http://www.cityoffrederick.com/cms/page/index.php?id=547).

However, the committee urges the Army to go beyond risk communications and undertake genuine two-way community engagement, in which the general public, including the CLCAC, has the opportunity to identify, during the Army's and BSA Environmental Services's initial study phase, potential failure scenarios. Not only would such input improve the quality and completeness of the risk assessment, but it is also likely to strengthen community acceptance of the SSRA's findings. Risk communication should also include discussion of risk management plans that will minimize risk of a release event, such as proper training of laboratory workers. Although LAIs will always be a risk, it has been documented that cases have been substantially reduced with improvements in biosafety practices and training (e.g., see NRC 2010a, 2011c).

Communications should go beyond the explanation of risk and risk scenarios. The Army should explain exactly how risk findings will be incorporated into the design, construction, and operation of the MCMT&E facility. For example, the Army should describe how it will meet its obligations, under the National Environmental Policy Act, to evaluate genuine alternatives. The SSRA should clearly state the assumptions with respect to planned design and operation, including security and safety systems. It will be important to convey that the goal is not risk elimination but reducing the risk to an acceptable and manageable level and developing appropriate incident response plans for the acceptable risks. Furthermore, emphasizing the distinction of likelihood versus consequences in the assessment will help to place the SSRA in context, particularly because the facility design is only beginning. Almost all facility design elements focus on reducing the likelihood of adverse accidental or deliberate scenarios, not on the consequences. A scenario that is assessed to be of high risk but is high due to the potential consequences may not be as relevant for facility design considerations but would still be an important factor for consideration in the EIS.

If additional pathogens and countermeasures—beyond those reviewed in the initial risk assessment—are proposed for testing at the MCMT&E facility, who will be responsible for conducting and approving additional risk assessments? The committee has been told that MCMT&E's Institutional Biosafety Committee (IBC) may be responsible for reviewing and approving studies of organisms beyond those addressed in the initial risk assessment. If so, it is important that the general-public members on the IBC be identified publicly and be easily accessible to the public. The IBC should explain its charter, authority, and functions to the CLCAC.

In its previous letter report, the committee urged the Army to improve its communications with local doctors and hospitals, particularly to help community-based clinicians diagnose and treat unusual

infectious diseases. Given the possibility that some of the pathogens to be tested on MCMT&E animals might spread to household pets and farm animals in the area, it might also be advisable that local veterinarians receive training in the identification of such unusual infections among their animal patients.

In summary, the MCMT&E facility's communications with the public should go beyond reassurances that people are unlikely to get sick because of its operations. The Army should make it clear that it will listen to the public's concerns and use its risk findings to make the laboratory safer.

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ATTACHMENT A

Committee to Review Risk Assessment Approaches for the Medical Countermeasures Test and Evaluation Facility at Fort Detrick, Maryland

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Charles N. Haas is the L.D. Betz Chair Professor of Environmental Engineering and Head of the Department of Civil, Architectural, and Environmental Engineering at Drexel University. His broad research interests are in drinking-water treatment, bioterrorism, and risk assessment. Specific research activities include assessment of risks from exposures to deliberately released agents; engineering analysis and optimization of chemical decontamination schemes; microbiologic risks associated with pathogens in drinking water, biosolids, and foods; novel kinetic models for disinfection processes and process control; and use of computational fluid dynamics for process modeling. Dr. Haas is co-director of the Center for Advancing Microbial Risk Assessment that is jointly funded by the U.S. Department of Homeland Security and the U.S. Environmental Protection Agency. He received his M.S. from the Illinois Institute of Technology and his Ph.D. in environmental engineering from the University of Illinois. He was chair of the NRC Committee to Review the Health and Safety Risks of High-Biocontainment Laboratories at Fort Detrick.

Karen B. Byers is the biosafety officer at the Dana-Farber Cancer Institute where she oversees the research practices and training for Biosafety Levels 1-3 and Animal Biosafety Levels 1-3 laboratories. She is currently the president of the American Biological Safety Association and was the recipient of the association's Everett Hanel, Jr., Presidential Award in 2001 for promoting the field of biological safety and fostering the high professional standards of the association's membership. Ms. Byers received an M.S. in microbiology from the University of Maine in Orono. She is a registered biosafety professional and a certified biosafety professional.

Nancy D. Connell is professor and vice-chair for research in the Department of Medicine at the University of Medicine and Dentistry of New Jersey (UMDNJ), New Jersey Medical School. Her major research focus is the interaction between *Mycobacterium tuberculosis* and the macrophage. She directs the UMDNJ Center for Biodefense, which does research in drug discovery for select agents and in development of biodefense preparedness training programs. She chairs the Recombinant DNA Subcommittee of the Institutional Biosafety Committee and directs the Biosafety Level 3 Facility of the UMDNJ Center for the Study of Emerging and Re-emerging Pathogens. She received her Ph.D. in microbiology from Harvard University. Dr. Connell was a member of the NRC Committee to Review the Health and Safety Risks of High-Biocontainment Laboratories at Fort Detrick and currently serves on the Committee on Review of the Scientific Approaches Used During the FBI's Investigation of the 2001 Bacillus Anthracis Mailings and the Committee on Trends in Science and Technology Relevant to the Biological Weapons Convention: An International Workshop.

Sara Y. Del Valle is a scientist and project leader in the Decision Applications Division of the Los Alamos National Laboratory. She also holds an appointment as an adjunct research professor in the Department of Mathematics and Statistics at Arizona State University. Her research interests are in developing and analyzing mathematical models for the spread of infectious diseases, including smallpox, HIV, and influenza, on a pandemic scale. She has also worked on modeling, simulating, and analyzing large-scale, agent-based discrete-event simulations, including the Epidemic Simulation System, Multi-scale Integrated Information and Telecommunications System, and the Healthcare Simulation System. Dr. Del Valle received her Ph.D. in applied mathematics and computational sciences at the University of Iowa.

Joseph N.S. Eisenberg is associate professor in the Department of Epidemiology at the University of Michigan. His research interests are in infectious-disease epidemiology and development of disease-transmission models. Recent work focused on the development of a new microbial risk-assessment framework that shifts the traditional approach of individual-based static models to population-based

dynamic models. His work with the U.S. Environmental Protection Agency has involved applying these transmission models to assess the public-health risks from exposure to microbial agents in drinking waters, recreational waters, and biosolids. Dr. Eisenberg received his Ph.D. from the University of California at Berkeley and San Francisco.

Mark T. Hernandez is professor in the Department of Civil, Environmental, and Architectural Engineering at the University of Colorado at Boulder and is an active consultant to the indoor air quality sector. He is also faculty director and principal investigator at the Colorado Diversity Initiative. A generation of his research lies on the cusp between biological air pollution, waste-water treatment systems, and molecular biology. Recent work focused on tracking and characterizing bioaerosols generated by large-scale disasters, including major metropolitan floods, the quarantined City of New Orleans following Hurricanes Katrina and Rita, and coastal Louisiana affected by the Horizon oil spill. Dr. Hernandez serves as editor of the journal *Aerosol Science and Technology*. Dr. Hernandez received his B.S., M.S., and Ph.D. in environmental engineering from the University of California at Berkeley and is a registered professional civil engineer. Dr. Hernandez was a member of the NRC Committee to Review the Health and Safety Risks of High-Biocontainment Laboratories at Fort Detrick and currently serves on the Committee on the Evaluation of a Site-Specific Risk Assessment for the U.S. Department of Homeland Security's Planned National Bio- and Agro-Defense Facility in Manhattan, Kansas.

Leonard M. Siegel is director of the Center for Public Environmental Oversight (CPEO), a project of the Pacific Studies Center that facilitates public participation in the oversight of military environmental programs, federal facilities cleanup, and brownfield site revitalization. He is one of the environmental movement's leading experts on military facility contamination, community oversight of cleanup, and the vapor intrusion pathway. For his organization, he runs two Internet newsgroups: the Military Environmental Forum and the Brownfields Internet Forum. Mr. Siegel also serves on numerous advisory committees, including California's Brownfields Revitalization Advisory Group, the Interstate Technology and Regulatory Council's Permeable Reactive Barrier Work Team, the Department of Toxic Substances Control (California) External Advisory Group, and the Moffett Field (former Moffett Naval Air Station) Restoration Advisory Board. He has also served on several committees of the NRC, including the Committee to Review the Health and Safety Risks of High-Biocontainment Laboratories at Fort Detrick.

ATTACHMENT B

WORK PLAN

SITE-SPECIFIC RISK ASSESSMENT FOR THE MEDICAL COUNTERMEASURES TESTING AND EVALUATION FACILITY AT FORT DETRICK IN FREDERICK COUNTY, MARYLAND

Final | 15 July 2011

Prepared by: BSA Environmental Services, Inc.

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Project Description (Planning and Scoping Stage)

The project goal for the U.S. Army Medical Research and Materiel Command (USAMRMC) is to develop a site-specific risk assessment (SSRA) for the Medical Countermeasures Testing and Evaluation Facility (MCMT&EF) at Fort Detrick, MD. The risk assessment aims to document the likelihood, adverse consequences, and uncertainty of reasonably foreseeable events that can affect the health of people working in and around the laboratory as well as members of the community. Environmental impacts will be identified and characterized in the Environmental Impact Statement (EIS) that will include the SSRA as an appendix that addresses human health risks.

USAMRMC will be conducting vaccine and drug research for agents in the medical countermeasures portfolio. The SSRA will provide decision support for USAMRMC to address the adequacy of current controls and interventions protecting workers and preventing accidental releases that could cause human illness in the surrounding community. The SSRA will only address risk associated with acute health issues particular to the laboratory work conducted at MCMT&EF. Examples of possible intentional release scenarios will be consider within the constraints of the current Biosurety Program, regulations, and barriers for containment.

The risk assessment approach described below represents a tiered assessment consistent with current knowledge of disease for portfolio agents and key risk references (National Research Council [NRC], 2008 Science and Decisions; the International Life Sciences Institute framework for microbial risk assessment (International Life Sciences Institute [ILSI], 2000); and National Academy of Sciences [NAS] letter reports (2011 and others). The major objectives of the tiered assessment are:

- Compile and structure available scientific evidence on conditions necessary to cause disease (sources, stressors, populations, routes, pathways, endpoints; Figure 1) and provide transparency regarding knowledge and gaps for portfolio agents listed below:
    - *Bacillus anthracis* (anthrax)
    - *Brucella spp.* (brucellosis)
    - Ebola/Marburg viruses (viral hemorrhagic fevers)
    - *Francisella tularensis* (tularemia)
    - Venezuelan Equine Encephalitis (VEE)/ *Eastern Equine Encephalitis* (EEE)/ Western Equine Encephalitis (WEE) viruses (febrile disease, encephalitis)
    - *Yersinia pestis* (plague)
- Conduct a comprehensive review of contemporary scientific literature and publically available information from national surveys to identify risks, hazards and mitigation processes associated with laboratory acquired illnesses for above listed pathogens, transmission to the community, intentional and accidental release, transportation release, work with animal species anticipated at MCMT&E, and the development and testing of vaccines and countermeasures
- Construct reasonably foreseeable scenarios (possible scenarios hereafter) consistent with mechanisms of disease and knowledge of dose-response

relationships for likelihood and severity of disease given exposure, considering source, stressors (agents), populations, route, pathway, and endpoint (see Figure 1, including illustrative examples for tularemia)

- Develop conceptual model for analysis (see Figure 2)
- Characterize human health risk qualitatively (unlikely or possible)
- Identify possible scenarios amenable to quantitative analysis
- Develop and run exposure assessment and dose-response assessment models to characterize human health risks, with attendant uncertainty (qualitative narrative)
- Prepare risk communication materials from qualitative and quantitative results
- Document future expansions for consideration as new data become available

As previously stated (March 21st presentation to the NAS panel), agent-specific evidence for disease mechanisms will be considered for defining plausible agent and route combinations. If the qualitative risk assessment (QualRA) results in 'unlikely' determination for either the exposure assessment or the dose-response assessment, the pathway or hypothetical scenario may be implausible. In light of the high level of community interest for the MCMT&EF, our strategy is to meticulously communicate what is known (and what is unknown) to preclude misleading the public, particularly when feared scenarios are implausible. For example, available evidence supports quantitative modeling of the exposure pathways for Ebola by the dermal/percutaneous route for laboratory workers, not ingestion and mucosal/ocular routes (see Appendix Figure A-3). Pathways determined unlikely in the QualRA for each agent would not be modeled due to inconsistency with current knowledge of mechanisms of disease, as scientific rigor may be insufficient to support modeling for the possible inhalation route for this agent.

Scientific evidence will be structured to support both tiers (qualitative and quantitative) risk assessment. Structural evidence will be used to estimate unlikely and possible scenarios for QualRA and frequency and consequences of possible scenarios. Both approaches will address confidence measures representing uncertainties. Quantitative risk assessment (QuantRA) will be employed as a second tier of analysis when first-tier qualitative assessments cannot confidently bound scenario risks as ‘unlikely’ and sufficient data are available to support a quantitative assessment that significantly improves risk characterization. Gaps in scientific knowledge and research in progress will be noted as appropriate in uncertainty analyses.

1) Approach for Qualitative Risk Assessment

The approach was developed based on knowledge of microbial risk assessment frameworks (e.g., ILSI, 2000), as well as published and ongoing research informing biothreat risk assessment, supplemented by targeted searches of the literature to identify additional relevant published studies for the pathogens in the current agent portfolio. Sections 2 and 3 of the work plan present our approach with specific examples for tularemia due to the concern of the local community and the recent laboratory

associated tularemia infection. For completeness and transparency, approaches planned for other agents in portfolio are outlined briefly in Appendix 1.

A) Hazard Identification for Tularemia

Tularemia is a zoonotic disease (an animal disease that can be transmitted to humans) caused by the Gram negative coccobacillus Francisella tularensis. This agent is thought to infect up to 250 animal hosts, more than any other known zoonotic pathogen (Dempsey et al., 2006). Contact with the following animals is associated with cases of human tularemia: beavers; cats; crayfish; dogs; dormice; hamsters; hogs and wild boars; mule deer; muskrats; non-human primates (NHPs); pheasants; prairie dogs; wild rabbits and hares; sheep; and squirrels. Tularemia is endemic in the U.S. (including Maryland) and around the world and is thought to persist in nature in enzootic cycles involving wild mammals (largely rodents, rabbits, and hares) and arthropod vectors (ticks, mosquitoes, flies) or amoeba.

Evidence for the disease triangle or triad (pathogen, host, and environment, with interactions) influencing disease likelihood and severity) was compiled for tularemia as outlined below. Human tularemia is characterized by abrupt onset of febrile illness (fever and flu-like symptoms) that is often self-limiting and rarely fatal. Human cases from laboratory acquired infections (LAIs), clusters of sporadic cases, and outbreak cases were considered, as well as clinical studies in humans and NHPs, the most relevant animal models to humans anatomically and physiologically. Key studies include the following: Saslaw et al. 1961; Eigelsbach et al. 1962; Eigelsbach et al. 1968; Dahlstrand et al. 1971; Schricker et al., 1972; Martone and Marshall et al. 1979; Deverill et al. 1996; Feldman et al. 2003; Siret et al. 2006; Twenhafel et al. 2009; and Hauri et al. 2010. Also considered in development of this work plan are a consensus statement published in the medical literature (Dennis et al. 2001) and reviews by Adamovicz et al. (2006), the World Health Organization (WHO) (2007), Lyons and Wu (2007), and Sinclair et al. (2008).

a) Pathogen
   (i) Major F. tularensis subspecies or biotypes causing human illness include:
      - Subspecies tularensis (Schu S4)
      - Subspecies holarctica (425; attenuated live vaccine strain)
   (ii) Fastidious and slow-growing bacteria requiring cysteine and sulfhydryl compounds; unlikely to grow in the environment outside of hosts and vectors
b) Host
   (i) Describe
      - Typically occurring in previously healthy adults
         - Workers in laboratory, landscaping, hunting and trapping, agriculture (farmers, hay handlers, herders, ranchers)
         - Butchers, campers, cooks (game meats), sugar factory workers, veterinarians, walkers
      - Little knowledge for more susceptible populations
         - Outbreak data include middle aged adults and some children and elderly adults

- Occasional isolations from hospitalized febrile patients with underlying conditions (neutrophil deficiency; immunosuppression due to organ transplant, cancer, HIV; or the presence of a prosthetic medical device) from endemic areas
- Human vs. NHP data

c) Environment
   (i) Consider factors and pathways influencing viability, infectivity, and persistence of strains in various environments
      - Factors include humidity, temperature, ultraviolet radiation exposure
   (ii) Consider representativeness of experimental conditions to hypothetical releases
      - Pathways by route

d) Interactions (conditions necessary to cause cases or disease outbreaks)
   (i) Tularemia is endemic worldwide, and human outbreaks are often associated with outbreaks in wild animal populations from direct contact with infected or dead animals or contaminated fecal material in air or water. Tularemia is perpetuated in complex enzootic cycles between wild mammals (predominantly rodents, rabbits, and hares) and invertebrates (~50 species of arthropods including ticks, mosquitoes, flies) and amoeba
   (ii) Present state of knowledge for mechanisms of host-pathogen interactions as illustrated in Figure 1. Temporal and spatial patterns of disease and disease progression for human and zoonotic disease will be addressed.
      - Incubation period before onset of disease; time to detection in lymph nodes, blood, lungs and pleura, spleen, liver, and kidneys; influence of innate and adaptive immunity, with and without vaccination; time to death; global distribution and severity
      - Human clinical disease forms
         - Outbreaks or clustered exposures commonly ulceroglandular (frequently by tick or mosquito vectors or contact with infected animals or die-offs (e.g., voles, mice, rabbits, muskrats)
         - Less commonly oropharyngeal following ingestion of food or water contaminated by infected or dead animals or feces
         - Rare ocular associated with direct contact with infected pets or other animals or by transmittal on fingertips after handling an infected or dead animal
         - Rare pneumonic disease outbreaks from contaminated agricultural dusts (landscapers in Martha's vineyard, Swedish agricultural workers), contaminated aerosols from infected hares among participants in a hunt in Germany, and uncertain aerosol source infecting vacationers at a renovated mill in France
   (iii) Routes of human exposure
      - Primary (inhalation; ingestion; dermal/percutaneous; ocular/mucosal)
      - Secondary (no evidence for person-to-person or monkey-to-monkey transmission)

(iv) Describe estimated occupational exposures (for laboratory workers, hunters, landscapers, agricultural workers) and estimated exposures to community members
- Describe bounds for exposures, e.g., U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) maximum production volume of culture slurries (20 mL per batch culture, USAMRIID 2008. Agent Information Sheet for ciprofloxacin-resistant F. tularensis)

(v) Summarize sources of dose-response data and tabulate results by stressor (pathogen strain), population (and host), route, pathway, and endpoint causing mortality, illness, and no illness (Figure 1 for illustrative examples regarding tularemia; Appendix 1 for other agents in portfolio)

(vi) Identify unlikely and possible scenarios

B) Problem Formulation

a) Develop conceptual models by agent, as illustrated in Figure 2, incorporating data collection and analysis from hazard identification and other information as needed

b) Define objectives and key variables for inclusion

(i) LAIs
- Rate declining. For unspecified facilities, USAMRIID reported 225 cases prior to 1976, 2 deaths; for unspecified laboratories, WHO reported declining rates of LAIs from 5.7 cases per 1,000 workers in the 1950s to 0.3 cases per 1,000 workers in the 1960s
- Risk mitigations for workers and community (e.g., training materials identify high risk activities; personal protective equipment; laboratory containment equipment and design specifications (e.g., negative pressure); autoclaving)
- Recent LAIs generated by uncertain errors or deviations from protocols without transmission in community

(ii) Define stability limits in air and water
- Short-distance aerosol pathways (plumes/puffs) may be possible (pneumonic tularemia is rare, despite endemic presence and high experimental infectivity in humans and NHPs)
- Short-distance water-borne pathways may be possible
- Long-term exposures unlikely

(iii) Define boundaries for selected accidental and intentional releases as possible scenarios that are reasonably foreseeable events during operation of MCMT&EF

c) Describe key variables (populations, routes, pathways) for exclusion and rationale

(i) Indoor air for community

(ii) Outdoor air for workers

(iii) Ingestion for workers

(iv) Dermal/percutaneous for community

(v) Mucosal/ocular transmission for workers (in personal protective equipment [PPE]) and community

(vi) Secondary transmission

(vii)Vector transmission

d) Describe inputs, outputs, data sources, data quality and quantity, methods of analysis, data gaps, and inferences, assumptions or judgments
   (i) Describe relationships in common language and in mathematical terms

C) Technical Analysis (qualitative)

a) Conduct exposure analysis
   (i) Describe evidence on exposure routes and pathways and discuss unlikely and possible scenarios for human tularemia cases in workers and the community (populations)
   (ii) Survival and decline by pathway
   (iii) Derive boundaries for magnitude, frequency, and duration of human exposures for possible scenarios
   (iv) Provide rationale for possible and unlikely scenarios
   (v) Identify data gaps
   (vi) Other issues TBD
b) Conduct dose-response analysis
   (i) Describe evidence for dose-dependencies, for populations, routes, pathways, and endpoints (what we know and what we don't know about human tularemia dose-response relationships)
      - Address resistance to illness (asymptomatic illness)
      - Address susceptibility to illness (mild/moderate/severe/fatal illness); reported quantitative measures include infective doses (IDs) for exposed volunteers and IDs and or lethal doses (LDs) for animals exposed in clinical studies
         - ID_{50}s (inhalation) in humans ~100 and in NHPs ~50
         - ID_{50}s (ingestion) in humans and NHPs $>10^6$ and $<10^8$ (no illness in NHPs at 10^4)
         - LD_{50}s (inhalation) in humans unknown and in NHPs ~50 and $>10^6$
      - Report incubation periods, duration and severity of illness
   (ii) Identify data gaps
   (iii) Other issues TBD
c) Conduct risk characterization
   (i) Compare outputs of exposure assessment and dose-response assessment to estimate the likelihood and severity for human morbidity and mortality for possible scenarios
   (ii) Prepare narrative summaries of results
   (iii) Describe sources of uncertainty and impacts on risk estimates
d) Prepare risk communication materials

2) Approach for Quantitative Risk Assessment

A) Problem Formulation

a) As mentioned above, QuantRA will be employed as a second tier of analysis for scenarios first-tier qualitative assessments cannot confidently bound scenario risks as "unlikely", and there is data to support a quantitative assessment that significantly improves the characterization of risk.
   (i) Approaches to QuantRA for complex systems can be subdivided between fine-grained and course-grained methods.
      - Fine-grained methods typically attempt to characterize risk and consequences of a scenario through detailed representations of system state changes. They are computationally intensive, require large amounts of data for parameterization and validation, and are often non-transparent because of their complexity and the platform specific aspects of their implementations.
      - Course-grained methods, sometimes referred to as semi-quantitative methods, typically use simple quantitative models that are more transparent but less exhaustive. We have determined that the course-grained approach is the preferred methodology for most of the current risk assessment for several reasons.

b) Because of the limitations on the data available for the agents in the scope of this risk assessment and many open scientific questions regarding both the biology and the computational methodologies, we do not expect fine-grained methods to adequately reduce uncertainties in risk characterizations relative to course-grained methods.

c) Since the primary goal of the scenario analyses will be to document scenarios and pathways with risk and consequences that will need mitigation and management, we feel the more-transparent course-grained methodologies will do the most appropriate for this assessment

B) Technical Analysis and Modeling

a) Structure and simulate possible exposure scenarios
   (i) Estimate magnitude, frequency, and duration of human exposures based on available evidence
   (ii) Identify the patterns and distribution of health consequences for exposure scenarios
   (iii) Address uncertainties for data and impacts of assumptions
   (iv) Identify data gaps
   (v) Other issues TBD

b) Model dose-response relationships for likelihood and severity of human and NHP illness based on key studies
   (i) Address uncertainties for extrapolations (pathogen strain, host, endpoint)
   (ii) Identify data gaps
   (iii) Other issues TBD

c) Conduct risk characterization

(i) Integrate outputs of exposure assessment and dose-response assessment to estimate the likelihood of human health effects (mortality or survival) for possible scenarios
(ii) Prepare summaries of simulation results
(iii) Conduct uncertainty and sensitivity analyses
(iv) Note influential data gaps and assumptions and provide interpretation

d) Prepare risk communication materials
   (i) Risks will be presented in the context of existing background risks for accidental zoonotic disease transmission and other risks in daily life (community and occupational risks; auto accidents, heart disease…)
   (ii) Three common concerns are often raised in the evaluation of quantitative risk assessments: the completeness/comprehensiveness of the analysis; the scrutability/transparency of the analysis for independent evaluation; and the quantification and communication of uncertainty and sensitivity in risk estimates. While an ideal risk assessment will be comprehensive, transparent, and strongly validated, practical logistic constraints must also be considered to prepare a thorough and timely analysis fit-to-purpose, in this case, appropriate to support USAMRMC decisions. We are aware of competing interests for this project, including interests and concerns of the NAS committee and the community. Our plan includes full consideration of recommendations of both groups in Section 2, as appropriate. For example, extensive literature for dose response data and models is available, only data relevant to the potential exposure will be reviewed. Rather, the team will build on published sources for existing models or key datasets judged most influential and relevant biologically for predicting human disease. Specifically, our rationale is to focus on primate data due to anatomical, physiological, and immunological similarities for deposition and clearance of agents more representative of human systems than rodents, until mechanistic models in development for anthrax (Gutting et al., 2008) and tularemia (McClellan, 2009) are available for more definitive extrapolations. The team will also focus on boundary analysis where competing assumptions are not validated experimentally. In this manner, the tiered analysis will build on what is known scientifically and acknowledge gaps that limit credible predictions
   (iii) The value of QuantRA for a biological laboratory is limited by uncertainties in the importance of many factors. This is not unusual, it has been identified as a problem in risk assessments from the nuclear and space programs since at least the 1970's. What is unusual is that the laboratory facilities being evaluated have missions that are specifically aimed at reducing these uncertainties. To reduce uncertainty, laboratories are needed which may contribute to the very risk we are seeking to manage. This is not an irreconcilable issue, but a reality needing acknowledgement

3) Quality Assurance

Working documents and results of analyses will be available to all team members on project File Transfer Protocol (FTP) site. One team member will draft sections and analyses, and a different team member will review the draft for accuracy and transparency. Final reports will be reviewed by the team prior to other quality control checks overseen by BSA Environmental Services Inc.

A) Quality will be ensured in each step

a) Citation of scientific metrics (and their limitations) from epidemiologic and clinical literature, with particular emphasis on body of literature from LAIs
b) Rationale for qualitative and quantitative analyses (inclusions and exclusions)
c) Clear identification of assumptions and expert opinions where direct scientific evidence is lacking or weak

B) The work plan, intermediate results, and final reports will be provided to USAMRMC as scheduled

4) Milestones and Deliverables

The following work plan summary is proposed for assessing progress toward completion of final report to USAMRMC.

Table 1. Work Plan Summary

Stage	Deliverable or Section	Specific Tasks/Activities
Planning and Scoping	Work Plan Conceptual Model	▪ Articulate goals, breadth, depth or complexity, focus, and boundaries of risk assessment for MCMT&EF o Exclude consideration of dry powders, vectors, genetically engineered agents as per current portfolio (acknowledge uncertainties about future) o Identify reasonably foreseeable event scenarios and exclude unlikely scenarios based on knowledge of biology of agents in portfolio and diseases they cause o Ensure transparency in distinguishing between scientific evidence, simulation results, and expert opinions for modeling potential risks o Consider demographic information on workers and nearby communities to inform o Present highlights of relevant case studies (biosurety, biocrimes, zoonotics) ▪ Identify competing values (e.g., timeliness vs complexity and resource burden) ▪ Frame direct and mitigation-related hazard identification for workers and the community potentially exposed to the six agent classes currently included in portfolio for MCMT&E, including LAIs ▪ Develop strategy for agent-based tiered assessment o Tier I: qualitative analysis for agents in current portfolio for medical countermeasure testing and evaluation o Tier II: quantitative analysis for selected agent/route/pathway/endpoint combinations judged to represent reasonably foreseeable event scenarios (considering disease mechanisms) ▪ Draft figures, tables, and text communicating scope ▪ Commit to schedule and budget, and future reassessments ▪ Develop and implement conceptual model to frame qualitative and quantitative analysis
QualRA	Problem Formulation Hazard Identification Exposure Analysis Dose-Response Analysis Risk Characterization Interim Report	▪ Consider data and methods for stages of risk assessment (exposure assessment; dose-response assessment; risk characterization) ▪ Conduct direct and mitigation-related hazard identification for workers and the community potentially exposed to the six agent classes currently included in portfolio for MCMT&E ▪ Stratify agents by plausible combinations (routes and mechanisms) for scenario development in exposure assessment ▪ Address Biosurety Program, Regulations and barriers for containment ▪ Draft figures, tables, and text communicating results; organize results into report sections or appendices
	Risk Communication	▪ Develop products for communicating what is known, and what is not known, at this stage of the risk assessment process

QuantRA	Technical Analysis Exposure Analysis Dose-Response Analysis Risk Characterization Interim Report	▪ Build and vet explicit list of exposure scenarios for modeling to team (and USAMRIID?); run models and vet outputs to team ▪ Implement existing dose-response models for explicit list of scenarios; vet outputs to team ▪ Combine exposure assessment and dose-response assessment outputs to characterize risks for explicit scenarios; vet outputs to team ▪ Draft figures, tables, and text communicating results; organize results into report sections or appendices
	Risk Communication	▪ Develop products for communicating what is known, and what is not known, at this stage of the risk assessment process
SSRA	Final Report	▪ Combine interim QualRA and QuantRA reports with executive summary ▪ Submit and prepare responses to comments from USAMRMC and NAS peer review o NAS charge to assess the adequacy and validity of the proposed risk assessment methodology and the draft results of any assessments to be incorporated into the EIS ▪ Update final report for public release ▪ Brief with USAMRMC at public meeting
Additional Cycles of Analysis and Deliberation		▪ Consider needs and resources for updating or expanding analysis as new products for T&E develop

Table 2. Major Elements of Analysis Plan (Box 3-4, NRC 2008)

Sources	*Obtaining and analyzing information on the sources in the analysis (e.g., source location, important release parameters)* ▪ Accidental exposure in laboratory ▪ Accidental or intentional release from laboratory
Agent (Pollutants)	*Confirming agents of interest and estimating potential exposure values* Agent list for current portfolio for medical countermeasure T&E ▪ Literature uploaded on FTP site
Exposure pathways and routes	*Assessing exposure pathways and ambient exposures* ▪ Conditions for laboratory infections by agent o Primary and secondary engineering of facilities to prevent release from a lab and the facility; rates of failure o Primary containment (PPE) to protect workers o Biosurety to prevent intentional releases (insider) o Facility security to prevent intentional releases (outsider) o Training to prevent inadvertent exposures; reporting of spills, accidents and illnesses to seek immediate medical care to prevent illness or rapidly treat illness o Recent multi-system failures i.e. Center for Disease Control (CDC) lightning strike/generator problem o Theft, loss or release during transport and records pertaining to transport related problems o Discussion of how state public health lab, citizens committee, and general public will be notified of accidents, releases, illnesses (each may receive different amounts, granularity of information and at different times) o Discussion of how local clinicians will be brought up to speed on atypical agents worked with at MCMT&E and how/what type of assistance USAMRIID doc's can provide in case of community illness sparking 'worried well' panic. o Conditions for zoonotic infections (sporadic and outbreak) by agent o Stability in air, water, fomites, infected animals and other matrices, and potential influences of weather on rates for transmission and survival o Epidemiologic data available for the selected agents in laboratories and in natural environments in Frederick County, MD or adjacent areas
Exposed populations(s)	*Characterizing populations of interest and estimating exposures including temporal and spatial variables* ▪ Workers contacting cultures, aerosols, or infected animals with and without mitigating protections in laboratories o History of LAIs from public sources o Contemporary data comparison of LAI from USAMRIID records and public records ▪ Community members downwind from deliberate or accidental release of agents o For agents expected to persist in aerosol environments for temporal

	and spatial boundaries derived from available literature ▪ Qualitative discussion of literature on variability in human (Hattis, 1999, 2001) and primate (Martonen 2001) respiratory exposure and response, including what is known about susceptible populations
End points (morbidity, mortality)	*Proposed sources of evidence on pathogenicity and virulence of agents and risk metrics* ▪ Published relevant literature on nature and severity of diseases in humans, laboratory animals, and wildlife as appropriate from clinical and epidemiologic studies (e.g., CAMRA, CIDRAP, SERRA) ▪ Primary research publications as needed o No illness if rate of clearance exceeds rate of deposition, more likely for lower doses o Metrics for morbidity may include febrile illness with or without defined fever index o Metrics for mortality may require qualitative or bounding analyses acknowledging uncertainty and potential bias for extrapolation ▪ Reliable rates in animals from controlled experiments, but with uncertain validity in predicting fatal disease in humans ▪ Rates unreliable in humans (doses, numbers exposed unknown; case-fatality rates outbreak specific)

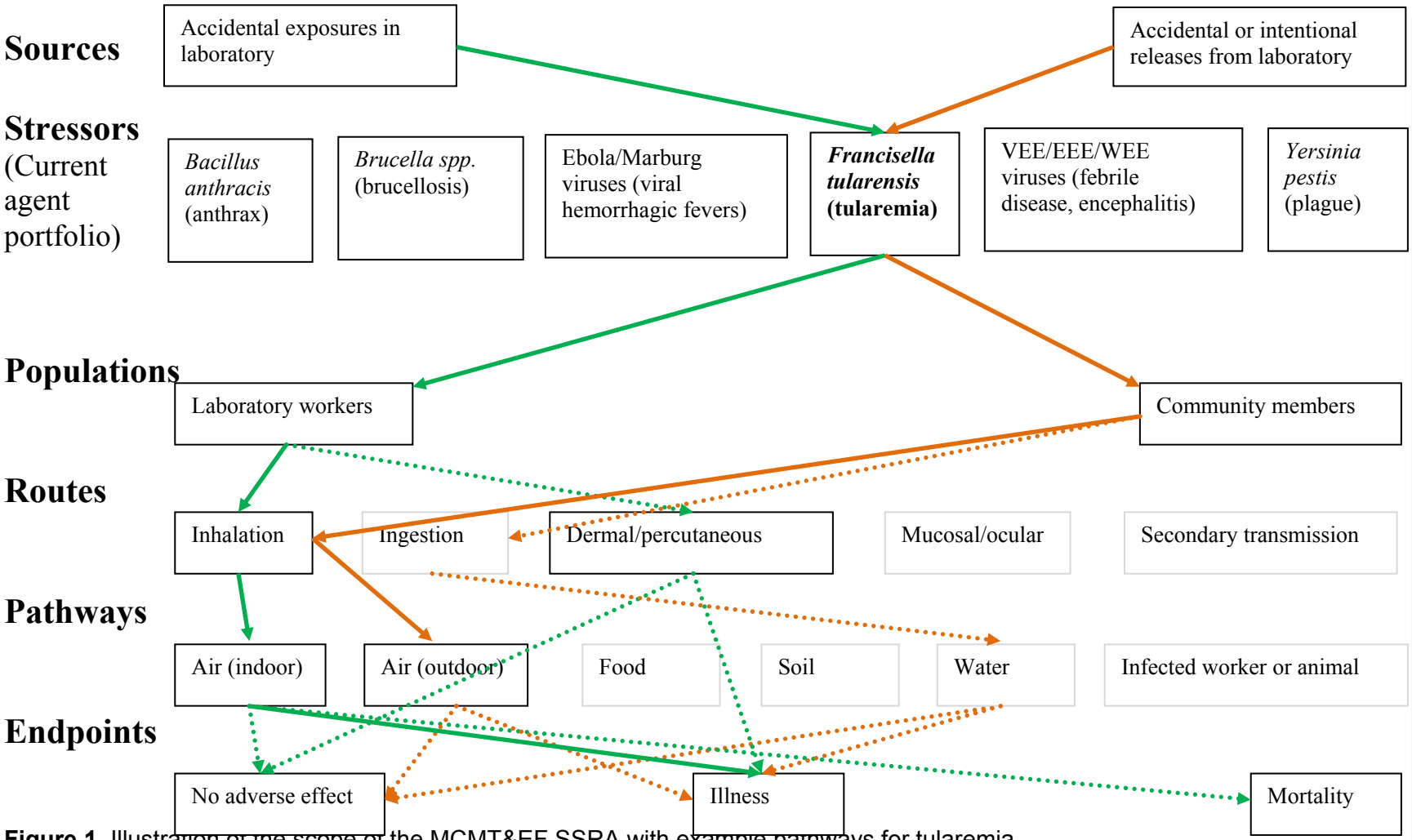

Figure 1. Illustration of the scope of the MCMT&EF SSRA with example pathways for tularemia

Figure 1 legend. The scope of the MCMT&EF SSRA is illustrated, as adapted from Science and Decisions (NRC, 2008; Figure 3-2). Lines linking boxes represent example linkages for tularemia scenarios. Solid lines indicate scenarios for recent observations of LAIs and outbreaks, dashed lines indicate possible scenarios, and boxes without connecting lines indicate unlikely scenarios that are excluded from quantitative analysis. Rationale will be provided in QualRA section of the SSRA report for the scenarios considered and excluded. **Source**s are indicated by green lines for accidental exposures in laboratories and orange lines for accidental or intentional releases from the laboratory. **Stressors** are the current agent portfolio. **Populations** are laboratory workers or community members, as will be discussed in detail in the hazard identification of the SSRA report. **Routes** are agent specific and include primary (inhalation, ingestion, dermal/percutaneous, mucosal/ocular) and secondary transmission. **Pathways** are agent-specific and include air, food, soil, water, and an infected worker or animal. **Endpoints** include no adverse effect, illness, or mortality.

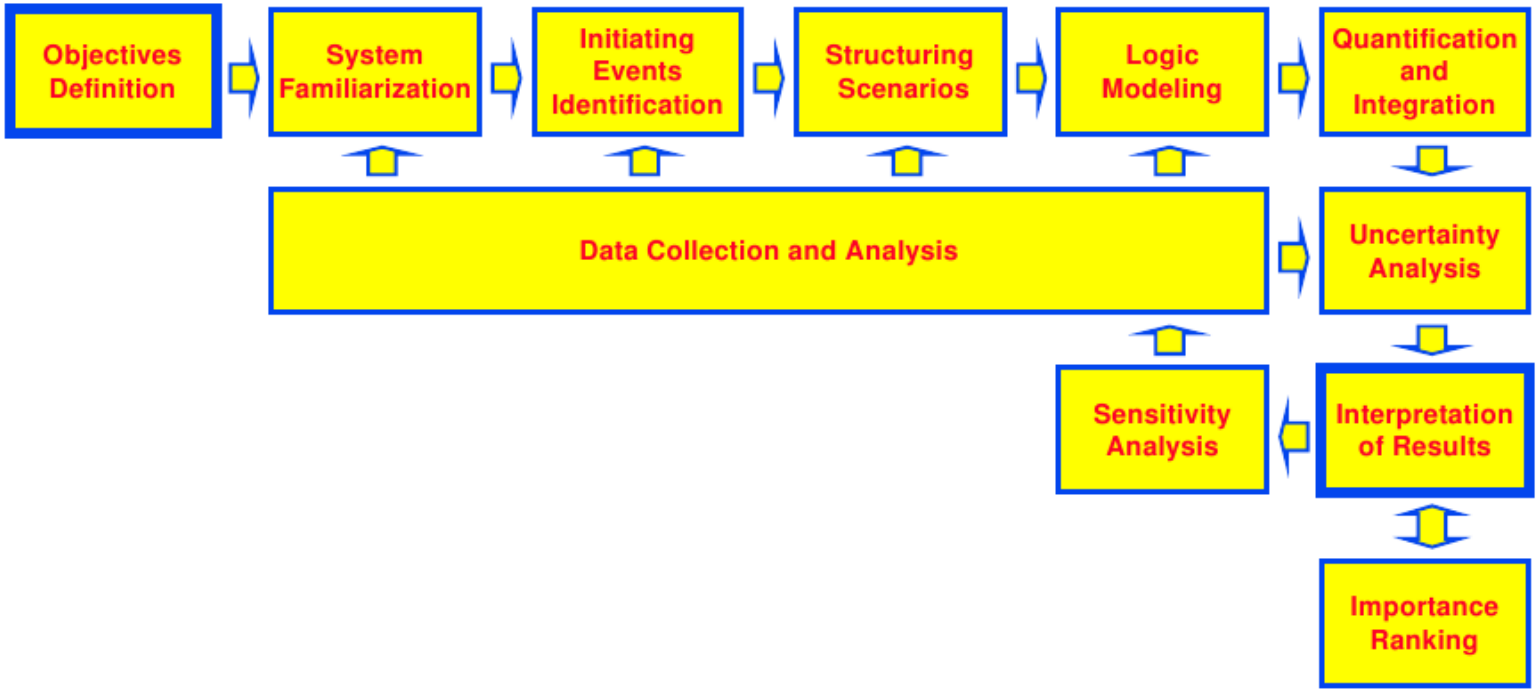

Figure 2. Typical probabilistic risk assessment task flow (Figure 3-13; NASA *Probabilistic Risk Assessment Procedures Guide for NASA Managers and Practitioners.*) The work flow of a probabilistic risk assessment is a cyclic process. Once the objectives and perspectives of the PRA are defined, the first step is a period of familiarization with the system under study. This familiarization period is needed to assist in the identification of initiating events that will be the risk assessment. For each initiating event, scenarios are structured, and then modeled as sets of logical pathways leading up to a consequential event and determining the consequences that follow. The likelihoods and impacts of these pathways are then quantified and integrated to determine risk under the preferred metrics, and the uncertainty of these risk metrics is documented based on the pathway identification and quantification. All of these steps incorporate data collection and analysis in various forms. The risks determined for each scenario are then interpreted and critiqued. The sensitivity of the results to the model assumptions should be considered, potentially initiating another round of initiating-event identification and scenario analysis. When needed, risks may be rank in terms of importance to assist in action and decision prioritization.

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Acronyms and Abbreviations

CDC	Center for Disease Control
EEE	*Eastern Equine Encephalitis*
EIS	Environmental Impact Statement
FTP	File Transfer Protocol
ID	infectious dose
ILSI	International Life Sciences Institute
LAIs	laboratory acquired infections
LD	lethal dose
MCMT&EF	Medical Countermeasures Testing and Evaluation Facility
NAS	National Academy of Sciences
NHP	non-human primates
NRC	National Research Council
PPE	personal protective equipment
QualRA	Qualitative Risk Assessment
QuanRA	Quantitative Risk Assessment
SSRA	Site-specific Risk Assessment
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USAMRMC	U.S. Army Medical Research and Materiel Command
VEE	Venezuelan Equine Encephalitis
WEE	Western Equine Encephalitis
WHO	World Health Organization

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Appendix 1. Additional Planning by Agent based on Figure 3-2 of Science and Decisions (NRC 2008)

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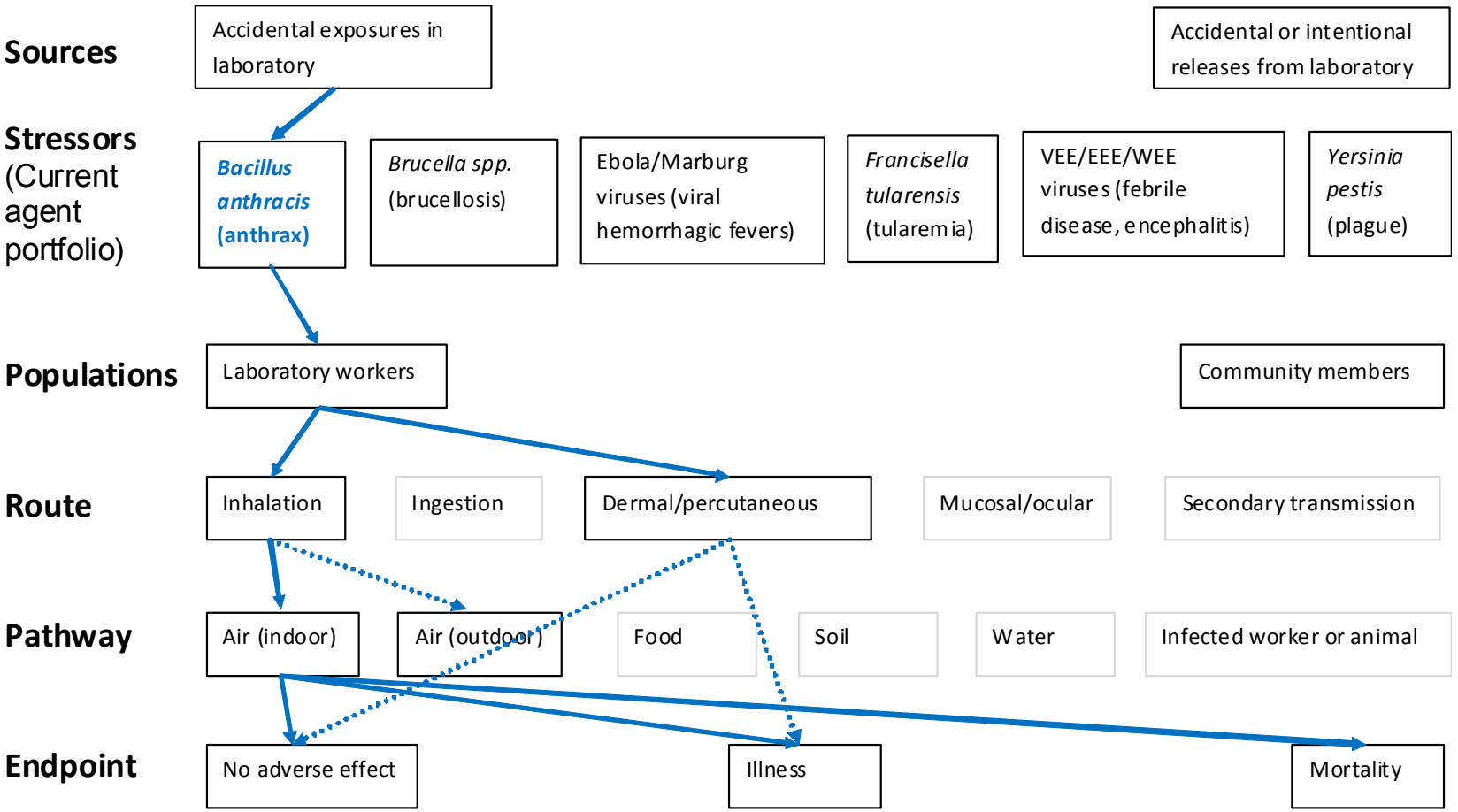

Figure A-1. Scope of microbial risk assessment for current portfolio of agents planned for MCMT&EF. For anthrax from accidental exposures in the laboratory, pathways are identified by solid blue lines for observed exposures in recent laboratory associated infections (LAIs) and by dashed blue lines for possible exposures. Unlikely scenarios are excluded (gray text box borders). Supporting evidence and rationale will be provided for all pathways in the qualitative risk assessment section.

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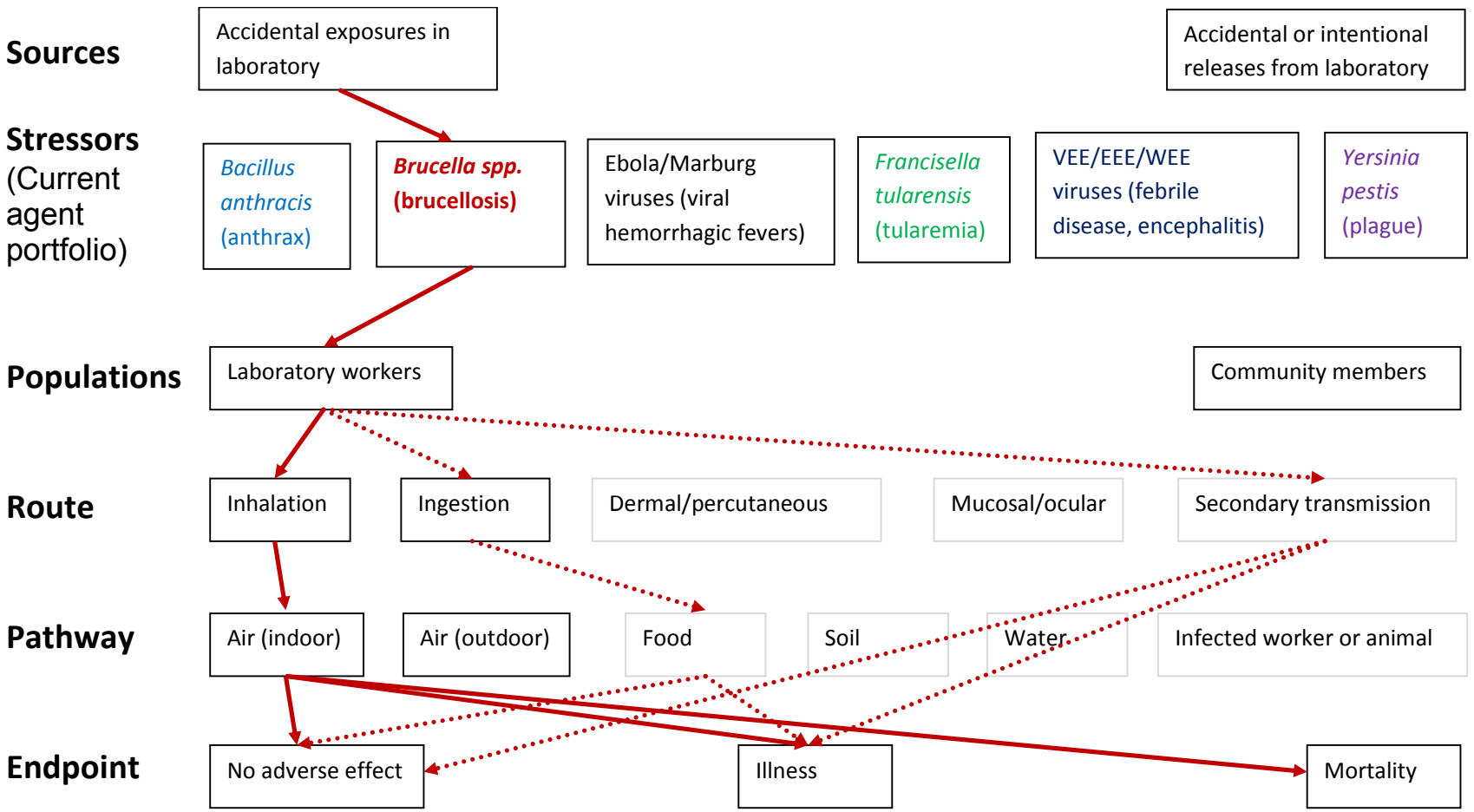

Figure A-2. Scope of microbial risk assessment for current portfolio of agents planned for MCMT&EF. For brucellosis from accidental exposures in the laboratory, pathways are identified by solid red lines for observed exposures in recent laboratory associated infections (LAIs) and by dashed red lines for possible exposures. Unlikely scenarios are excluded (gray text box borders). Supporting evidence and rationale will be provided for all pathways in the qualitative risk assessment section.

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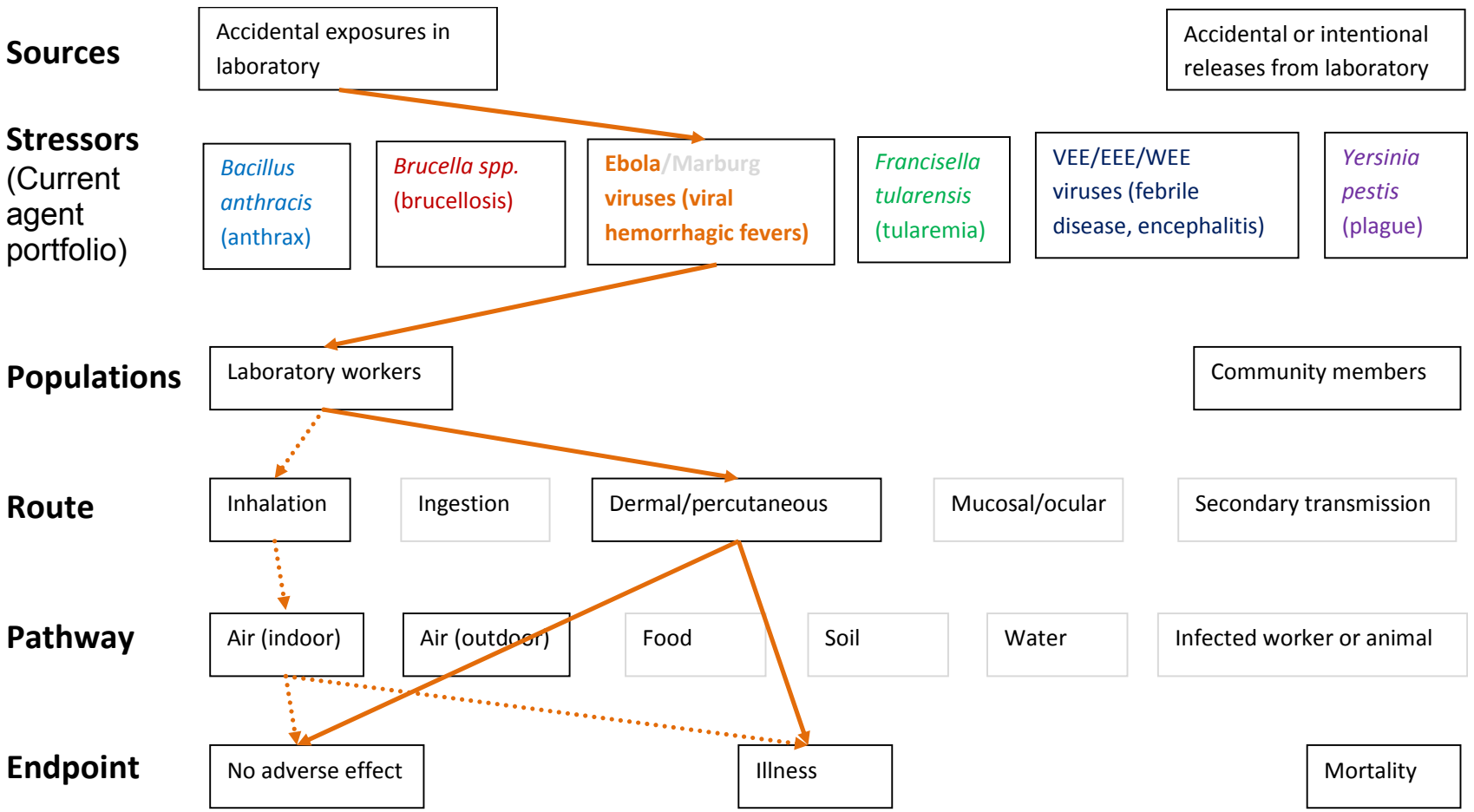

Figure A-3. Scope of microbial risk assessment for current portfolio of agents planned for MCMT&EF. For Ebola infections from accidental exposures in the laboratory, pathways are identified by solid orange lines for observed exposures in recent laboratory associated infections (LAIs) and by dashed orange lines for possible exposures. Unlikely scenarios are excluded (gray text box borders). Supporting evidence and rationale will be provided for all pathways in the qualitative risk assessment section.

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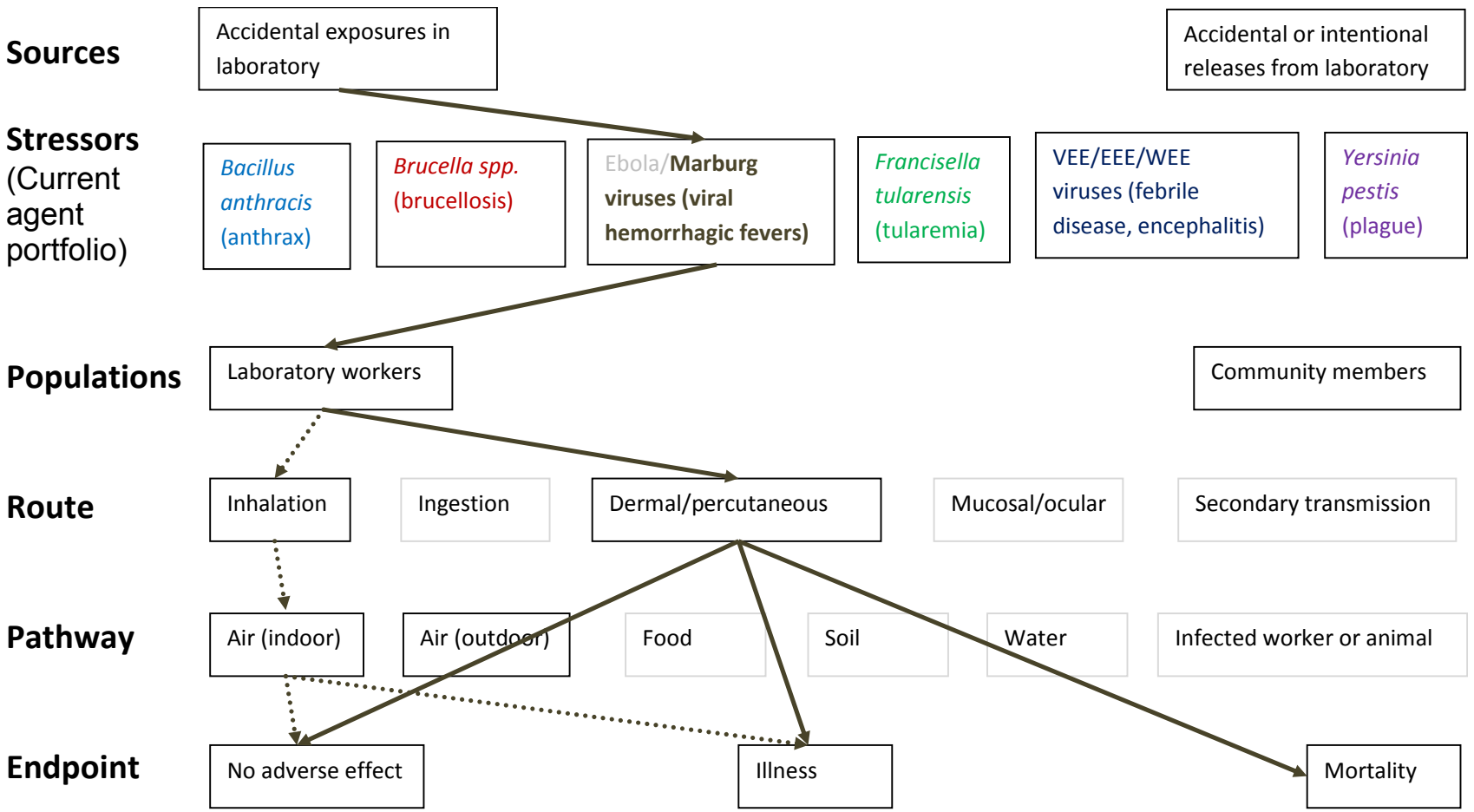

Figure A-4. Scope of microbial risk assessment for current portfolio of agents planned for MCMT&EF. For Marburg infections from accidental exposures in the laboratory, pathways are identified by solid brown lines for observed exposures in recent laboratory associated infections (LAIs) and by dashed brown lines for possible exposures. Unlikely scenarios are excluded (gray text box borders). Supporting evidence and rationale will be provided for all pathways in the qualitative risk assessment section.

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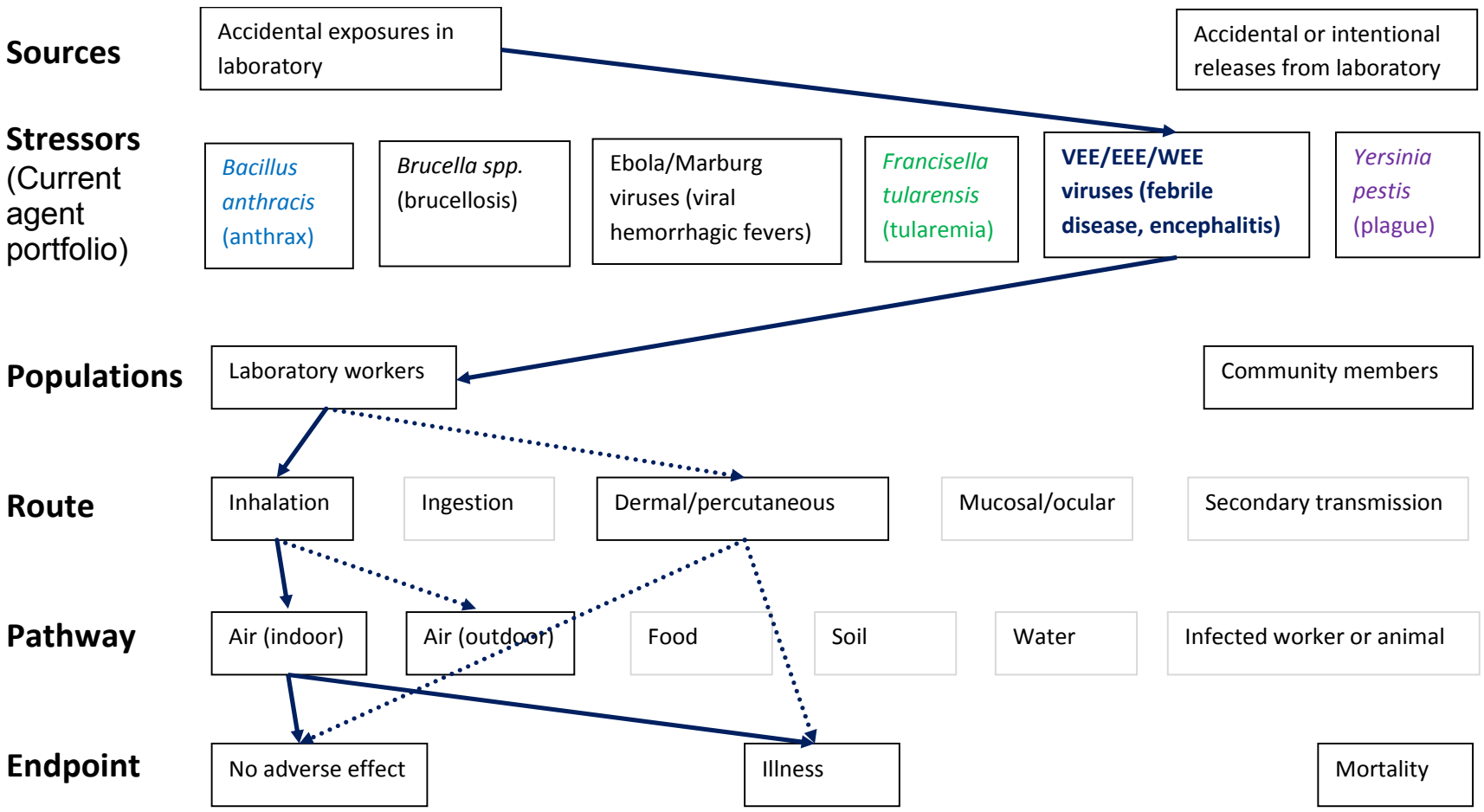

Figure A-5. Scope of microbial risk assessment for current portfolio of agents planned for MCMT&EF. For encephalytic infections from accidental exposures in the laboratory, pathways are identified by solid dark blue lines for observed exposures in recent laboratory associated infections (LAIs) and by dashed dark blue lines for possible exposures. Unlikely scenarios are excluded (gray text box borders). Supporting evidence and rationale will be provided for all pathways in the qualitative risk assessment section.

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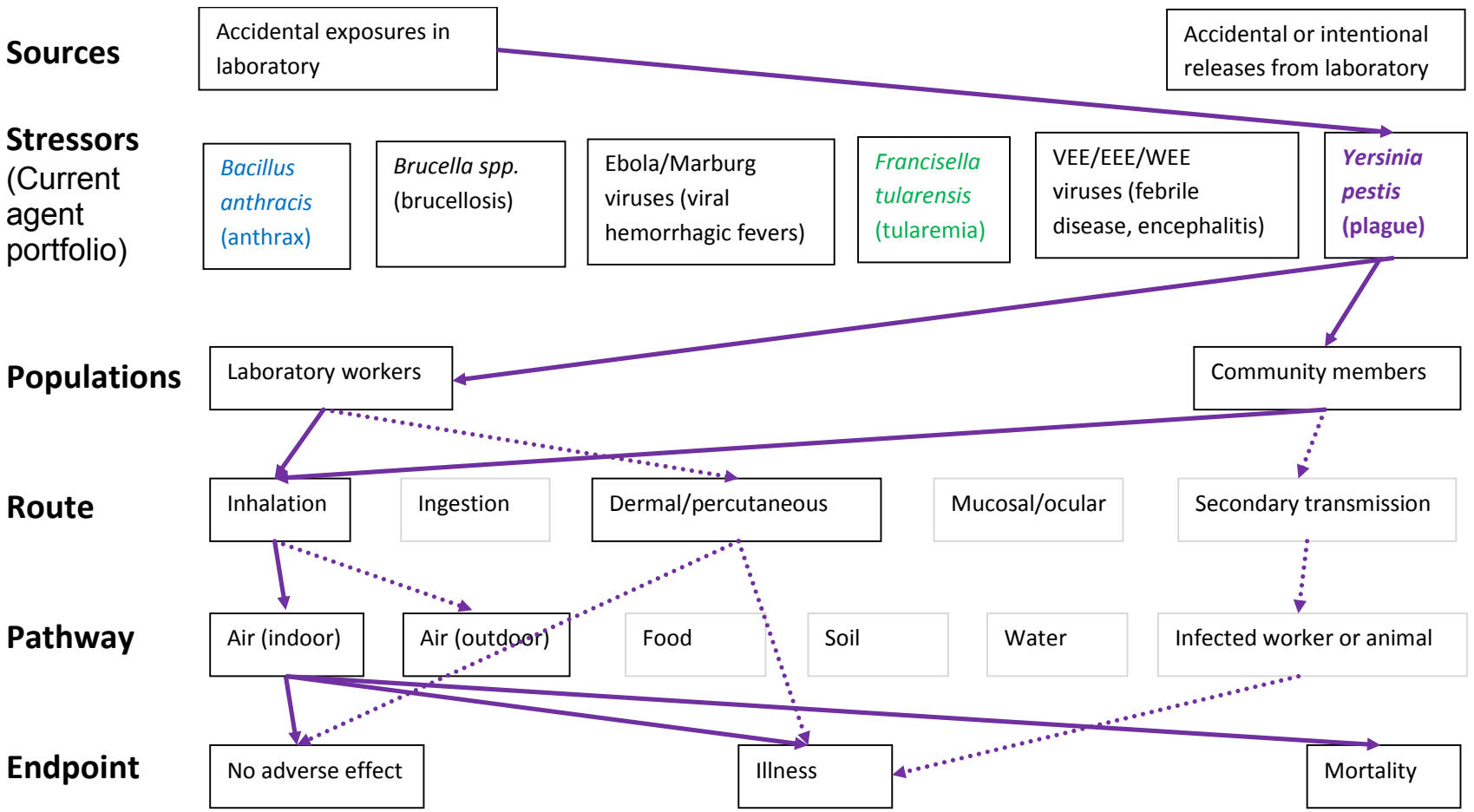

Figure A-6. Scope of microbial risk assessment for current portfolio of agents planned for MCMT&EF. For plague infections from accidental exposures in the laboratory, pathways are identified by solid purple lines for observed exposures in recent laboratory associated infections (LAIs) and by dashed purple lines for possible exposures. Unlikely scenarios are excluded (gray text box borders). Supporting evidence and rationale will be provided for all pathways in the qualitative risk assessment section.

ATTACHMENT C

Reviewer Acknowledgements

The report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of the independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Edward Perrin, University of Washington. Appointed by the National Research Council, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility of the final content of this report rests entirely with the authoring committee and the institution.