Assistance to the U.S. Army Medical Research and Materiel Command with Preparation of a Risk Assessment for the Medical Countermeasures Test and Evaluation (MCMT&E) Facility at Fort Detrick, MD: A Letter Report

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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
Washington, DC 20001

April 27, 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 risk assessments for the new biocontainment laboratory at the base. Enclosed is the committee's first letter report on the Army contractor's proposed approaches to conducting the risk assessment.

On behalf of the committee, we look forward to the progress made toward completing the risk assessment and providing a review of that effort later this year.

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

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 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 biocontainment laboratories, as well as procedures and regulations for their operation. The committee found that USAMRIID's 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 the EIS being prepared for the MCMT&E facility. Technical input could include, but not be limited to, a review of the proposed work plan for preparing risk assessments, as well as information on the selection of pathogen agents, scenarios, and models to be used in the risk assessments. If the preliminary model results for the quantitative risk assessment and the qualitative assessments were available, they would be reviewed. The committee was not asked to perform an independent evaluation of the safety of the MCMT&E facility or the EIS as a whole but was asked to 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 committee's full Statement of Task is provided in Attachment A.

The Army requested that the former NRC committee that performed the USAMRIID review be reconvened to the extent possible to review plans for the risk assessment of the MCMT&E facility. Five

[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.

members of the previous committee agreed to serve on the current committee, and three new members were added to supplement their expertise (see Attachment B for biographic information on the members). The committee held its first meeting on March 21-22, 2011 (see Attachment C for the agenda of the public portion of the meeting). Army representatives and contractors provided an overview of the MCMT&E program and presented the proposed approach to the SSRA. An open microphone session was held to hear from the Frederick County community about its concerns. The committee's evaluation was also informed by the work of other NRC committees involved in similar reviews of biocontainment facilities (NRC 2007, 2008, 2010a,b,c,d).

This letter report presents the committee's evaluation of the Army contractor's proposed approach to conducting an SSRA for the MCMT&E facility. The approach was documented in briefing slides and discussed at the March meeting (see Attachment D). The committee did not review the plans for any other aspects of the EIS. The committee will review work performed toward the SSRA and issue a second letter report on its findings later this year. This report reflects the consensus of the committee and has been reviewed in accordance with standard NRC review procedures (see Attachment E).

OVERALL ASSESSMENT OF THE SSRA BRIEFING

The committee compliments the Army for involving outside review of the SSRA process prior to the implementation of a work plan for the risk assessment. This review is an atypical task for NRC committees, which are more commonly tasked with reviewing full reports or documents. The Army contractor's SSRA plans are at the early stage of conceptualizing the agents, sources, receptors, exposure pathways, and potential adverse human health effects. The next step should be to specify the analytic and interpretive approaches for the risk assessment (see NRC 2009). Other agencies, such as the U.S. Environmental Protection Agency (EPA 2004), and previous NRC reports (e.g., NRC 2009) have defined the major elements that are required for a work plan (see Box 1). After the March 21 meeting, the Army was asked whether the committee's comments should be directed to helping develop a formal work plan, with the understanding that the committee's second task would be to review that more detailed plan. The Army's response was that the Power Point slides (Attachment D) were in fact the work plan, and the expectation was that the committee would review the completed risk assessment as its second task (J. Souris, USAMRMC, personal communication, March 22, 2011). In the opinion of the committee, the briefing slides do not contain the critical elements delineated in Box 1 to fully evaluate the proposed scope of work. In the absence of a formal work plan and preliminary facility designs, it was difficult to assess whether the Army contractor's approach will result in a comprehensive and credible SSRA. Therefore, the committee has approached its task by describing significant critical elements that are important for executing a successful SSRA. When the SSRA is completed, it should be sufficiently detailed and transparent so that one can understand (1) the criteria and rationale for making choices about scenarios (e.g., agents and routes of exposure), (2) the rationale for determining whether quantitative or qualitative analyses were performed, and (3) the choice of models, parameters, sensitivity analyses, and uncertainty analyses for independent verification. The remainder of this letter elaborates on these points.

A key element of doing a risk assessment is problem formulation, a technically oriented process for operationally structuring the assessment (NRC 2009). A reasonable expression of the problem for scoping the risk assessment might be, "What are the residual risks to the workers and general public from projected operations at the proposed MCMT&E facility?" The term "residual risk" is used to describe the risk remaining after design, engineering, and operational controls are considered (including their performance characteristics). Hence, 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.

The MCMT&E facility SSRA will be based on a specific scope of operations. The facility is intended to serve outside entities, such as pharmaceutical companies, on a fee-for-service basis, so it is likely that it will be asked to undertake activities not envisioned during the scoping process. Because such activities might alter the risk associated with the facility, the Army should describe, up front, the threshold of change in operations that would trigger the need to conduct a supplemental EIS and risk assessment.

Box 1. Example of Major Elements of an Analysis Plan

Sources	How will information on the sources in the analysis (e.g., source location and important release parameters) be obtained and analyzed?
Pollutants	How will agents (chemical or biologic) be confirmed and their emission values be estimated?
Exposure pathways	How will the identified exposure pathways be assessed? How will ambient concentrations be estimated?
Exposed populations	How will exposures to populations of interest be characterized? How will their exposure concentrations be estimated? What will be the temporal resolution? What sensitive populations may be affected?
End points	How will information on the toxicity or pathogenicity of agents be obtained (what are the data sources)? What risk metrics will be derived for the risk characterization?

In addressing the above aspects of the analysis, the plan should also clearly describe the following:

- How will quality be ensured in each step? For example, what will be included in the quality assurance and quality control plans?
- How will uncertainty and variability in the results be assessed?
- How will all stages of the assessment be documented?
- Who are the participants and what are their roles and responsibilities in the various activities?
- What is the schedule for each step (including milestone steps)?
- What are the resources (e.g., time, money, and personnel) being allocated for each step?

Source: Adapted from EPA (2004), as cited in NRC (2009).

SPECIFIC FINDINGS ON THE SSRA BRIEFING

Selection of Agents

The SSRA briefing listed eight organisms (*Bacillus anthracis*; *Ebola*, Marburg; *Francisella tularensis*; *Brucella*; arboviruses (three); and *Yersinia pestis* (slide 6 in Attachment D) to be included in the risk assessment for laboratory personnel and the general public. These agents were purported to represent "classes" of agents based on their characteristics, such as persistence, route of infection, characteristics of infection (disease), and planned research activities. The rationale and methodology for selecting these agents was not offered or justified. For example, three viruses belonging to the *Alphavirus* genus having the same transmission cycle were listed; the committee finds that inconsistent with the classification approach described. More than 20 other known agents, as well as other emerging pathogens and unanticipated threat agents, may be tested in the future, so it will be important for the SSRA to specify the strategy that was used to select representative agents. One approach recommended by a

previous committee (NRC 2010c) was a systematic characterization of the pathogens in the laboratory's current research portfolio. For example, a summary table of all the agents could be prepared that lists the following characteristics with the best available information and full citations:

- Known median infective doses for all infection routes (humans and animals).
- Contagiousness (e.g., pathogen load and shedding rates).
- Stability under different environmental conditions (e.g., temperature, light, pH, desiccation, humidity, and life-cycle status).
- Incubation period (humans and animals).
- Infectious period (humans and animals).
- Modes of transmission.

Although some of that information may not be available for all pathogens, it is important to document data gaps to help inform decision making. The information in the table should be used to develop a rationale for selecting a diverse, representative set of agents to include in the SSRA (see additional guidance on agent selection provided in NRC 2007, 2008, 2010c). For example, the SSRA briefing indicated that person-to-person transmission modeling would be performed for *Y. pestis*, but no justification was provided for why this bacterium was chosen as the example. Influenza viruses, such as H1N1, are much more transmissible than *Y. pestis* and would be better models of person-to-person transmission. However, it is unclear whether influenza viruses are in the research portfolio for the MCMT&E facility or whether other considerations have been factored into the selection. Describing the selection strategy in the SSRA will make it transparent how the agents were chosen.

One of the missions of the medical countermeasures program is to develop strategies for countering "naturally occurring (emerging) or man-made/released" threats (Ludwig 2011). The facility is designed for 31 years of operation, so the risk assessment should recognize the need for long-term planning for "unknowns." In the committee's estimation, there are three types of unknowns that should be considered. The first are biologic agents that are not in the current research portfolio, such as pathogen strains with altered phenotypes (antibiotic-resistant, vaccine-defeating, or "hypervirulent" strains), pathogen spillover to humans from other species, prions and other small biologically active molecules, and agents synthesized for malevolent intent. The second type of unknowns are compounds used in medical-enabling technologies (such as nanoparticle delivery systems, encapsulation, and molecular details of neural networks) and in physiologic control mechanisms, which might pose threats that lie outside traditional concepts of infectious agents (IOM 2006). The third are the countermeasures being developed at the MCMT&E facility. Certain vectors used in vaccines have recently been linked to cases of disease. For example, vaccinia virus (the live viral component of smallpox vaccine) has been linked to laboratory-acquired infections (LAIs) (CDC 2009) and secondary and tertiary transfer (CDC 2004, 2007; Hughes et al. 2011), and the first case of laboratory-acquired cowpox infection was recently reported in a worker exposed to a recombinant cowpox virus strain (Reardon 2011). Most biocontainment facilities establish review processes to consider these types of emerging threats. Thus, the risk assessment should disclose what the review process will be for considering the risk from emerging threats as they arise. For example, if the facility's Institutional Biosafety Committee will be responsible for assessing new threats (biologic or chemical) and establishing requirements for their safe handling, that should be disclosed.

Exposure Assessment

Scenarios

The SSRA briefing did not include detailed exposure-assessment plans, so it was difficult for the committee to ascertain how comprehensive they will be. The SSRA should include infrastructure work

plans, such as those that would be found in the civil engineering sector. As recommended in previous NRC (2010a,c) reports, release scenarios can be categorized into four pathways of exposure: (1) in air, (2) in solid waste, (3) in liquid waste and sanitary wastewater, and (4) in or on fomites or hosts. Critical release analyses for each of the fundamental pathways should include facility engineering, personnel reliability, and operational considerations (NRC 2010c). There are five areas where further assessment might be needed in the SSRA plan:

- *Primary Exposure Scenarios* consider contact with the potential agents and agent countermeasures, individually and in combinations.
- *Infrastructure-Based Analyses* follow the transport and fate of all agents and agent countermeasures in residuals that exit the facility as aerosols, liquids, and solid wastes.
- *Transporter Scenarios* follow the transport and fate of all agents and agent countermeasures in and on persons, animals, insects, and shipments that cross the facility boundary.
- *Dry-Use Scenarios* specifically follow the use, transport, and fate of all agents or agent countermeasures that are handled in a desiccated state.
- *Probabilistic Safety Analyses* consider possible natural hazards, human accidents, engineering accidents (internal and external), and utility failures in cascading, parallel, and series failure scenarios.

As noted above in Selection of Agents , it is important to provide a supporting rationale for selecting representative agents to be used in *primary exposure scenarios.* In addition to considering the agents individually, pathways that might result in exposure to multiple agents (possible co-infection) or agent countermeasures or to multiple receptors (people and animals), whether simultaneous or serial, should be explored.

For *infrastructure-based exposure analyses*, the potential fate of agents entrained on *all* environmental residual pathways (and the potential negative environmental or health effects of their intended countermeasures) should be quantified if possible. Residuals management is a paramount infrastructure issue from a containment and treatment perspective, particularly when animals are involved. Residuals are defined as (bio)aerosols, solid wastes (including animal carcasses), liquid waste, and sanitary flows (sewage and associated wastewaters) generated by the MCMT&E facility operations. Aerosol and waste-treatment transport pathways should be presented completely, and parallel infrastructure and state-of-the-art practices of experimental-animal facilities with similar charters should be consulted.

The SSRA should consider *transporter scenarios* where the transport of agents, or their intended countermeasures, can occur in or on other living things or are otherwise facilitated by shipments. The spectrum of transport routes includes all persons, animals, insects, and shipments that can cross the new facility's boundary.

The SSRA briefing stated that "drying equipment will be specifically and intentionally excluded from the facility" (slide 8 of Attachment D); therefore, no consideration of the *dry-use scenario* is necessary. However, the committee finds that this generalization could introduce oversight that limits risk perspective to the manufacture of dry powders within the proposed facility. It is conceivable that any number of dry formulations (including substances used as agent countermeasures) could be provided from sources outside the facility to be reconstituted into liquid for testing, although there will be no administration via dry powder to animal subjects (G. Ludwig, USAMRMC, personal communication, March 21, 2011). Thus, it might be appropriate for the SSRA to include dry-use scenarios if the MCMT&E facility will work with powdered drug formulations, such as those used in nasal drug delivery systems (e.g., Ishikawa et al. 2002; Friebel and Steckel 2010).

The SSRA should include *probabilistic safety analyses*. Natural and man-made hazards and potential failure scenarios, such as internal flooding, should be considered (e.g., by use of formal event trees or fault trees. Examples of guidance on probabilistic risk-assessment techniques include Rasmussen (1981) and Kumamoto and Henley (1996). The briefing failed to consider the need for external and

internal systems redundancy, including local utility support (e.g., electricity and natural gas). Scenarios for cascading, parallel, and series failures were not considered in the assessment paradigm.

Approach to Evaluation

The SSRA exposure assessment should be sufficiently detailed and transparent so that one can understand (1) the decision-making criteria that will trigger the use of a qualitative versus quantitative analysis; (2) the formal methods to incorporate assessment of uncertainty, variability, and sensitivity (both parametric and structural); and (3) the formal methods to conduct a probabilistic safety analysis (e.g., cascading, parallel, and series failures; natural hazards; and loss of key utilities).

The qualitative approaches presented in the SSRA briefing were scenario driven and provide some detail on potential pathways of transmission. The approaches should be formalized and have sufficient detail so that they capture the possible transmission pathways of the selected agents (EPA 2004; NRC 2009). The proposed "tiered analysis" (slide 6 of Attachment D) should be defined and address questions such as the following:

- What is the role of a qualitative analysis and what are the decision-making criteria that trigger the use of a quantitative analysis?
- How will the assessment of data availability or what is known about a given agent be used in the decision-making process?
- Will models be chosen on the basis of defined processes (e.g., transmission pathways or population structure) or on the types of data that are available (e.g., dose-response and environmental conditions)?

Models will be used to describe transmission pathways. Two transmission pathways mentioned in the briefing were aerosol release and person-to-person transmission. The aerosol-release pathway should explicitly describe scenarios in which agents either infect those within the facility or are emitted from the facility. The latter aerosol scenario should include sensitivity to meteorologic conditions, such as how wind and rain may affect dispersal and persistence of the agent (NRC 2010c). The person-to-person pathway should include an evaluation of risk to sensitive populations (e.g., individuals with reduced immunocompetence and older people) (NRC 2010d), including those who work within the facilities, other parts of Fort Detrick, and those who live in the community. The person-to-person pathway should address the risk of secondary transmission to the community if an infected worker is unaware of being infected and is not identified as the primary index case (NRC 2010a). A third pathway involving exposure via water (e.g., groundwater and surface water) was not considered in the briefing (both with respect to biologic hazards and countermeasure agents). Given that the waste streams from animals within the facility can be significant, inclusion of this water pathway in the SSRA is important. The models that will be used to simulate different transmission routes (e.g., aerosol, person-to-person, and water-borne routes) should be specified to allow for an independent assessment of the model predictions. Mathematical and computational models that can incorporate different pathways and exogenous factors (e.g., rain), as well as spatial and demographic characteristics, are necessary to capture potential impacts.

The decision process for choosing the appropriate models that account for the transmission pathways should be formalized in the context of the specific scenarios that will be assessed. Particular attention should be placed on the interdependencies of the transmission pathways. The interdependencies of these pathways should be extended to consider overall or cumulative risks[2] (NRC 1994, 2009),

[2]"Cumulative risks" refer to "the combined risks from aggregate exposures to multiple agents or stressors" (EPA 2003).

including risks from the MCMT&E facility independently and in conjunction with other facilities on the National Interagency Biodefense Campus and within the community.

Once the models are chosen, formal methods to conduct uncertainty analyses should be developed. Although the parameter values may be estimated from historical epidemiologic data, there is always uncertainty in their values. Therefore, uncertainty related to model parameters should be assessed by using distributions or ranges. In addition to parametric uncertainty, sensitivity to model specification and parameter estimates should be formally evaluated. Distinct from uncertainty analysis, sensitivity analysis addresses the impact of highly variable parameters on the outcome. Specifically, the parametric sensitivity should consider both forward and backward sensitivity (Kumamoto and Henley 1996).

The committee recommends that the Army contractor perform probabilistic safety analyses for a wide variety of events (e.g., natural events, deliberate sabotage, loss of key utilities, cascading failures, parallel or series failures, and aircraft crashes) that may result in facility failures. Recent natural events, such as the earthquake in Japan followed by a tsunami, highlight the importance of identifying potential catastrophic failures that can result in large-population, infrastructure, and economic impacts. A probabilistic approach (e.g., an event-tree or binary-tree approach) may be used to estimate the likelihood of different hazards (e.g., based on topographic and meteorologic predictions) and their cascading-impacts failure (Rasmussen et al. 1981; Kumamoto and Henley 1996). On the basis of the results obtained from the probabilistic estimate of different hazards, more thorough analyses can be performed (e.g., the impact of a hurricane or an ice storm on availability of critical utility services). Cascading impacts of infrastructure failure may be a challenge due to dependencies and interdependencies among different sectors. Impact analyses of different hazards on infrastructure and their recovery operations may need to be coordinated with specific sectors.

Risks from Laboratory-Acquired Infections

The SSRA briefing did not define a general approach for evaluating the potential risks from LAIs to other workers or the general public. Baseline mitigations should be defined to determine residual risks to these populations. There are two areas of concern:

- *Risk to Laboratory Personnel*: Published reports of LAIs from the scientific literature and exposure incident reports should be used as hazard assessment tools and should form the basis of risk-assessment scenarios (NRC 2010a,c). Specific equipment-related exposure incidents have occurred from use of centrifuges, sonicators, aerosol-exposure devices, standard microbiologic techniques (e.g., pipetting), and microbial culture. Because the MCMT&E facility will be conducting experiments with laboratory animals, consideration should be given to scenarios in which workers or laboratory animals might accidentally be bitten or scratched. The SSRA also should include scenarios of exposure to individuals with altered susceptibility. Thus, the assessment should include accommodations for staff with increased susceptibility profiles (e.g., immunodeficiency, pregnancy, and iron-storage defects).
- *Risk to Community Case Studies*: There is a paucity of published data on infections originating in laboratories and being transferred into the community. Nonetheless, such cases should be carefully studied. Examples include
    - Infection of medical photographer with smallpox and transmission to mother (Hawkes 1979).
    - Transmission of *Brucella melitensis* from worker to spouse (Ruben et al. 1991).
    - Leak of Sabia virus from laboratory in Brazil (Lemonick and Park 1994).
    - Leak of Venezuelan equine encephalitis virus from laboratory in Colombia (Brault et al. 2001).
    - Severe acute respiratory syndrome (SARS) spread by infected workers (Enserink and Du 2004).
    - Occupational spread of *Bordetella pertussis* (CDC/NIH 2009).

- Release of foot-and-mouth disease from Pribright (UK-HSE 2007).

Risk Characterization

The final integrative step of a risk assessment is a risk characterization, which is a summative description of the consequences in a form that is most useful to stakeholders and decision makers (NRC 1983, 1994, 2009). For the SSRA, the metrics to be used for risk characterization have not been clearly delineated. There are multiple possible adverse consequences from a potential release of agents and agent countermeasures, including illnesses (morbidity), death (mortality), direct economic consequences, and indirect economic consequences

Even if only human-health consequences were to be used as the metric of characterization, it is not clear whether the end point of interest (to the decision makers and stakeholders) is mortality; morbidity (perhaps divided into mild, moderate, and severe cases); or perhaps an integrative measure, such as disability adjusted life years (Murray and Lopez 1994). The metrics for risk characterization should be explicitly delineated in the SSRA (see Box 1, EPA 2004). The committee cannot offer specific recommendations for the most appropriate risk-characterization metrics because it will depend on the decision criteria and the objectives and preferences of the decision makers and stakeholders.

Public Engagement

It is important to engage stakeholders throughout the risk assessment process to the extent feasible (PCCRARM 1997; NRC 2009). At the March 21, 2011, public meeting, thoughtful, constructive comments were provided by the community. At the meeting and in the past, the community members have repeatedly requested that risk evaluations for laboratory facilities at Fort Detrick include a comparative risk assessment with alternative locations, such as remote or sparsely populated areas. The NRC committee that evaluated the Army's USAMRIID facility at Fort Detrick was supportive of conducting such an exercise because it would help "[distinguish between] risks and factors that are dependent on siting location (for example, the potential for disease transmission to livestock and wildlife in rural settings that could result in zoonotic outbreaks, or the availability of medical and emergency personnel) and those that are independent of site (for example, risks of a malicious insider)" (2010a, p. 53). Such an analysis should be considered for the MCMT&E facility as a means of addressing the concerns of community stakeholders.

The committee is pleased that the Army will involve the Fort Detrick Containment Laboratory Community Advisory Committee in its plans for the MCT&E facility. The Army is urged to present any significant changes in the proposed operation of the facility, such as the introduction of additional pathogens, to the advisory committee. This procedure could be implemented through the establishment of formal, regular communications between the advisory committee and the MCMT&E facility's Institutional Biosafety Committee.

Another concern of the Frederick community is the ability of the health-care system to respond to a major outbreak. To address such concerns, a thorough analysis that assesses the impact of a localized outbreak on the health-care sector should be performed, including the impact of public reaction (e.g., the "worried well") on available resources. Highly stressed hospitals (e.g., high occupancy levels and understaffing) can pose a risk to quickly mitigating the spread of a disease. A finding from a previous NRC (2010a) committee that reviewed the USAMRIID laboratory at Fort Detrick was "the lack of readily available clinicians with the necessary specialized training to consult on the clinical diagnosis and treatment of unusual infectious diseases." The report made recommendations for possibly filling this gap that would be relevant to the MCMT&E facility.

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ATTACHMENT A

Statement of Task

An ad hoc committee of experts will review technical input to a new Environmental Impact Statement (EIS) to be prepared for the Medical Countermeasures Test and Evaluation Facility (MCMT&E). 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 assessments to be incorporated into the EIS.

ATTACHMENT B

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

Members

CHARLES N. HAAS (*Chair*), Drexel University, Philadelphia, Pennsylvania
KAREN B. BYERS, Dana-Farber Cancer Institute, Boston, Massachusetts
NANCY D. CONNELL, University of Medicine and Dentistry of New Jersey, Newark, New Jersey
SARA Y. DEL VALLE, Los Alamos National Laboratory, Los Alamos, New Mexico
JOSEPH N.S. EISENBERG, University of Michigan, Ann Arbor, Michigan
MARK T. HERNANDEZ, University of Colorado at Boulder, Boulder, Colorado
JONATHAN Y. RICHMOND, Jonathan Richmond and Associates, Southport, North Carolina
LEONARD M. SIEGEL, Center for Public Environmental Oversight, Mountain View, California

Staff

SUSAN N.J. MARTEL, Project Director
FRANCES E. SHARPLES, Director, Board on Life Sciences
RUTH E. CROSSGROVE, Senior Editor
MIRSADA KARALIC-LONCAREVIC, Manager, Technical Information Center
TAMARA DAWSON, Program Associate

Sponsor

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Biographies of the Committee

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 biologic 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 developing 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 biologic air pollution, wastewater 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*. He 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 Department of Homeland Security's Planned National Bio- and Agro-Defense Facility in Manhattan, Kansas.

Jonathan Y. Richmond is CEO of Jonathan Richmond and Associates, a biosafety consulting firm with a global clientele. Prior to starting his own firm, Dr. Richmond was the director of the Office of Health and Safety at the Centers for Disease Control and Prevention in Atlanta, Georgia. He is an international authority on biosafety and laboratory containment design. Dr. Richmond was trained as a geneticist, worked for 10 years as a research virologist, and has been involved in the field of biosafety for the past 32 years. He is the author of many scientific publications in microbiology; he has chaired many national symposia, edited numerous books, and is an international consultant to ministries of health on laboratory safety and training. He served as president of the American Biological Safety Association. Dr. Richmond received his M.S. in genetics from the University of Connecticut and his Ph.D. in genetics from Hahnemann University. He 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 Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University National Emerging Infectious Diseases Laboratories.

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 C

Public Meeting Agenda

NATIONAL RESEARCH COUNCIL
Committee to Review Risk Assessment Approaches for the
Medical Countermeasures Test & Evaluation Facility at Fort Detrick, Maryland

First Meeting: March 21, 2011
Holiday Inn Hotel & Conference Center at FSK Mall
5400 Holiday Drive
Frederick, Maryland

6:30	Registration for Public Session	
7:00	Welcome, Introductions, Process for Open Session	Dr. Charles Haas, Chair
7:10	Plans for the Medical Countermeasures and Test Facility	Dr. George Ludwig Deputy Chief of Research and Technology U.S. Army Medical Research and Materiel Command
7:25	Overview of Risk Assessment Plans for the MCT&E Facility	Dr. John Beaver, President BSA Environmental
8:40	Open Microphone	

Each speaker has a maximum time limit of 3 minutes. Accompanying written materials are encouraged.

9:30 Adjourn

ATTACHMENT D

Briefing Slides

Goal

- Our goal is to develop a SSRA that is comprehensive, transparent, and practical by focusing on reasonably foreseeable events, and maximum credible events that could cause adverse health effects to people working in and around the laboratory, members of the community and the environment
- Assembled a diverse team of highly qualified experts who will employ the best and most innovative methods, and are seeking guidance/concurrence on our approach from NAS to achieve this goal

Team

- BSA Environmental Services, Inc.
- Barbara Johnson, Ph.D.
- Barbara Reynolds, Ph.D.
- Edward Eitzen, M.D., M.P.H.
- Margaret Coleman, M.S.
- Timothy Reluga, Ph.D.
- Medical Modeler (TBD)
  - Suggestions from NAS?

Overview of Approach

- Present the **approach** to site-specific issues/risks topics that were stated in the final report for the "Evaluation of the Health and Safety Risks of the New U.S. Army Medical Research Institute of Infectious Disease (USAMRIID) High-Containment Facilities at Fort Detrick Maryland" by NAS
- The following slides present the issue/risk topics followed by the Proposed Quantitative and/or Qualitative approach
- Seeking NAS concurrence/comments on the approach on each issue/risk topic

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Overview of Approach

- Throughout the presentation, references to USAMRIID will be used to highlight that this new facility will operate using the increased safety procedures and policies that USAMRIID uses
- The MCMT&EF will establish similar agreements that USAMRIID has with local government and healthcare
- USAMRIID will not own or oversee the MCMT&EF

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Selection of Agents

Tiered Analysis: Quantitative & Qualitative Aspects

- Systematically stratify the risks of different pathogens to the general public and lab personnel by disease mechanism
  - *Bacillus anthracis* - Anthrax
  - Ebola/Marburg virus
  - *Francisella tularensis* - Tularemia
  - *Brucella* – Brucellosis
  - Arboviruses:
    - VEE - Venezuelan Equine Encephalitis
    - EEE - Eastern Equine Encephalitis
    - WEE - Western Equine Encephalitis
  - *Yersinia pestis* - Plague

Selection of Agents

- Focus modeling effort where evidence of plausible mechanisms exists for agent and route combinations, as illustrated below
  - Model aerosol release for anthrax, not tularemia
  - Model person-to-person transmission for plague, not anthrax or tularemia

Risk: Insider Terrorist Acts

Potential actions taken by a laboratory employee that may circumvent biosecurity measures and maliciously expose members of the community to infectious agents

Qualitative Approach:

- Anthrax findings:
  - Retrospective case review
  - Negate future occurrences as the use of dry powders is outside of the mission
    - Drying equipment will be specifically and intentionally excluded from the facility
- Identify a few other 'biocrimes' as case reviews that are possible

Risk: Insider Terrorist Acts

Mitigations:

- Biosurety Program: Current robust regulations
  - Biosafety
  - Biosecurity
  - Biological personnel reliability program
  - Agent Accountability

Risk: Aerosol Dispersal

Quantitative Approach

- Tier II for "Reasonably foreseeable"/Maximum Credible Events (MCE) scenarios
  - Target efforts for agent and disease mechanism
- Include appropriate quantitative measure of per-person risk
  - Order of magnitude estimates of initial external release and location of susceptible population

Risk: Aerosol Dispersal

Quantitative Approach

- Develop dispersal models (puff and/or plume models), acknowledge serious limitations
  - Inability to represent atmospheric mixing robustly
  - Uncertain viability/virulence of released agent after dilution and exposure to environmental stresses in atmosphere
  - Few known mechanisms for secondary-transmission, reservoir-human or human-human
    - Could at best provide bounds on possible severity of hypothetical releases

Risk: Aerosol Dispersal

Quantitative Approach

- Use puff and plume models in determining regions where surveillance will be important
- Model dilution and atmospheric decay based on agents and simulants
- Develop plausible secondary transmission scenarios
  - reservoir-human, human-human

Risk: Aerosol Dispersal

Example Approach

- Simulate, for agent and route combinations selected, solutions based on best available evidence
  - How likely is a release and how large would it be?
  - What's the risk that a release will cause an index case?
  - What's the risk of secondary transmissions and spread after an index case?

Risk: Escape of Infected Animal or Arthropod Vector

Qualitative Approach

- Address potential concerns that an escape leads to the establishment of pathogen in a native animal or vector reservoir and result in long-term elevation in disease risk to the general public
- Summarize statistics on releases that have occurred and the results

Risk: Mishaps During Biological Material Shipments

Qualitative Approach

- Analyze potential transport of Biological Select Agents and Toxins (BSAT) as part of the biosecurity chain-of-custody
  - Address whether/how shipping poses a risk to the community by accidental/intentional release, or diversion of BSAT
  - Review Regulatory Processes in Shipping
    - CDC Form 2 and process
    - CDC Division SAT Internal tracking/follow through
    - DOD Interim Guidance for Shipping BSAT 10/08

Risk: Outside Terrorist Acts

Qualitative Approach

- Develop outsider terrorist act scenarios considering
  - Engineering features of facility
  - Physical security of facility
    - Physical security of Fort Detrick
    - Site-specific characteristics
  - New regulatory requirements

Risk: Natural Phenomena

Qualitative Approach

- Develop natural disaster scenarios
  - Earthquakes, hurricanes, tornados
    - Frequency of events in the area
    - Wind shear that could cause airflow reversals

Consider mitigations

- Engineering features of facility
  - Statistics on past data of engineering failures (industry wide)

Risk: Environmental Contamination

Qualitative Approach

- Develop potential environmental exposure scenarios considering
  - Special indoor air quality engineering features
  - Special engineering features of the wastewater treatment system
    - MCMT&F Self-contained Steam Sterilization
    - FD Wastewater Treatment System
  - Performance of post-autoclave solid waste treatment systems, autoclave infrastructure and load testing
  - Statistics on past data of engineering failures (industry wide)

Risk to Laboratory Personnel

Qualitative Approach

- Review literature involving Laboratory Acquired Infections (LAIs)
  - Overview based on literature review of LAIs: exposures, infections, and outcomes
  - Overview of USAMRIID LAIs from 1979-2010 (Rusnak and Safety Office)

Risk to Laboratory Personnel

Qualitative Approach

- Summarize key case study exposures Involving BSAT at USAMRIID
  - Glanders (2000)- lack of Personal Protective Equipment (PPE) /gloves (?)
  - Ebola (2004)- needle stick working with animals
  - Tularemia (2009)- inadvertent aerosol/ improper use of biological safety cabinet (BSC) (?), no respirator
  - Periodic toxin exposures- ocular (Staphylococcal Enterotoxin B [SEB]?)

Risk to Laboratory Personnel

Qualitative Approach

- Analyze case studies and provide rationale for inclusion and exclusion as potential scenarios of concern
  - Needle stick/sharps
  - Inhalation (exposure to intentionally generated aerosol or inadvertent generation)
  - Ocular/mucosal splash or contact
  - Laboratory animal/vector exposure
  - Unknown route
  - Persons affected in adjacent work spaces

Risk to Laboratory Personnel

Qualitative Description

- Draft List of Exposure Scenarios most likely for person in the lab and community members (should illness be unreported). For Example:
  - Aerosol exposure to *Y. pestis, F. tularensis*: faulty BSC use, unrecognized illness, risk to community member
  - Needle stick Ebola or Marburg: medical containment suite (MCS) admission, possible risk to health care provider
  - Ocular exposures to *F. tularensis*: poor hand hygiene, no risk to community/risk for personnel
  - Mosquito bite VEE or WEE: unrecognized illness, local hospital care, risk to community/health provider
  - Cutaneous anthrax or tularemia to abraded skin: development of lesions, risk to family/community

Risk to Laboratory Personnel

Mitigating Exposures and LAIs

- Expand training and practice
  - Standard/special procedures per Biosafety in Microbiological and Biomedical Laboratories (BMBL)
  - Additional procedures per Department of the Army (DA)/USAMRIID
- Develop knowledge of lessons learned and their effectiveness (reduce incidents)
  - Where possible provide by year implemented and trigger event
  - Include environmental sampling in suites for *B. anthracis*

Risk to Laboratory Personnel

Mitigating Exposures and LAIs

- Standard/special engineering controls (primary containment; retracting needles) per BMBL
- Additional engineering controls per DA/USAMRIID
- Engineering controls prompted by lessons learned and their effectiveness (reduced incidents)
  - Where possible provide by year implemented and trigger event

Risk to Laboratory Personnel

Mitigating Exposures and LAIs

- Consider standard/special PPE per BMBL
  - Additional PPE per DA/USAMRIID
  - Augmented PPE prompted by lessons learned
    - Where possible provide by year implemented and trigger event

Risk to Laboratory Personnel

Mitigating LAIs

- Continue research and practice for effective pre-exposure Immunization
  - Recommended immunizations per BMBL
  - Additional immunizations per DA/USAMRIID
  - Efficacy data/break through cases involving immunizations
  - Vaccine Efficacy of immunizations
  - Reduction in LAIs since immunizations began
    - Rusnak papers

Risk to Laboratory Personnel

Mitigating LAIs

- Expand practice for post-exposure controls/reporting
  - Special Immunizations Program (SIP)
    - Describe SIP and reporting triggers
    - Describe SIP staffing on/off duty hours
    - Improvements since Nov 2009 to ensure prompt/appropriate 'self-reporting'
  - Transport of Laboratory Personnel Potentially Exposed to Infectious Agents From Fort Detrick, Frederick, MD to the National Institutes of Health Mark O. Hatfield Clinical Research Center, Bethesda, MD

Risk to Laboratory Personnel

Mitigating LAIs

- Consider biological accident and incident reporting
  - Describe how/when U.S. Army Medical Research and Materiel Command, Maryland Public Health Lab, CDC, Frederick Memorial Hospital, Press, and others will be notified of LAIs
  - Describe Memorandum of Agreements (MOAs) and/or written procedures
  - CDC Form 3

Risk to Laboratory Personnel

Mitigating LAIs

- Consider post-exposure medical evaluation, prophylaxis and follow up
  - Briefly describe diagnostic methods and Post-exposure prophylaxis (PEP)
  - Describe patient follow up
  - Efficacy data for treatment regimes
    - Pre-symptomatic (following high risk exposure)
    - Post-symptomatic

Risk to Laboratory Personnel

Mitigations

- Consider USAMRIID Biosafety Program
  - Briefly describe staffing, chain of reporting, roles/responsibilities
  - Training program
  - Proficiency demonstration/exams/records
  - BSL-4 Internship and approval to work
  - Special training provided
  - Non-compliance (reporting, remediation, retraining, removal)

Risk to Laboratory Personnel

Mitigations

- Consider annual incident response drills
  - Describe last two drills
  - What is the regulatory requirement
  - Who plays
  - Tabletop vs. live
  - Duration
  - Analysis of findings
  - Remedial activities and outcomes

Risk: Spread by an Infected Worker

Quantitative Modeling

- Develop Tier II modeling for transmission of disease from an infected laboratory worker to family or community members
  - Course of infection for the agent
  - Likely transmission patterns following the index case
  - Surveillance, mitigation and management of secondary infections
- Consider data sufficient for constructing a robust model with biological fidelity
- Derive quantitative estimates of the risks and consequences of secondary infections that may occur subsequent to index cases

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Risk: Spread by an Infected Worker

Consider Mitigations

- MOA between Garrison, FMH, Barquist, USAMRIID
- Garrison relationship with Frederick County Health Department
- Review how this information will be relayed to the local government and the media in a timely manner

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Cumulative Impacts

- Clarify intent of National Academy of Science Committee
  - Require cumulative risk over proposed life span of the building... To individuals in labs and the community?
  - Prepare quantitative and retrospective statistical analysis from i.e. 1991-2001 with and without anthrax letters, and 2001-2011 (as current as feasible)
    - Can eliminate anthrax letters from the future as powders will not be studied?

Public Engagement

- Promote credible public engagement incrementally beginning with the USAMRIID community panel
- Foster a communication approach that is accountable, respectful and ethical

MCMT&EF SSRA

- Comprehensive
- Transparent
- Practical

The views expressed are those of the authors and should not be construed to represent the positions of the Department of the Army or Department of Defense.

Questions?

- Does the committee concur:
  - With the approach to site-specific issues/risks topics that were stated in the final report for the "Evaluation of the Health and Safety Risks of the New USAMRIID High-Containment Facilities at Fort Detrick Maryland"?
  - That the approach will address the recommendations provided in the report?

The views expressed are those of the authors and should not be construed to represent the positions of the Department of the Army or Department of Defense.

ATTACHMENT E
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:

John Ahearn, Sigma Xi Center
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Donald A. Henderson, University of Pittsburgh Medical Center
Akula Venkatram, University of California, Riverside

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.