Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL, Phase 2

Committee on Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL

Board on Life Sciences
Division on Earth and Life Studies

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Washington, D.C.
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November 5, 2010

Francis Collins, M.D., Ph.D.
Director
National Institutes of Health
Building 1
9000 Rockville Pike
Bethesda, Maryland 20892

Dear Dr. Collins:

At your request, the National Research Council (NRC)[1] reconvened its Committee on Technical Input on Any Additional Studies to Assess Risk Associated with Operation of the National Emerging Infectious Diseases Laboratory (NEIDL), Boston University[2] to provide you and your Blue Ribbon Panel with further technical input on the scope and design of any additional studies that may be needed to assess the risks associated with the siting and operation of the NEIDL.

In particular, you asked the NRC committee to meet with the NIH Blue Ribbon Panel in public at key milestones in the development of the draft risk assessment. To this end, the NRC committee met in open session with the Blue Ribbon Panel on September 22, 2010 to hear presentations by NIH's contractors on the approaches they are taking to conduct the risk assessment. Following the open meeting, the NRC committee met in closed session to begin preparing this brief letter report, focusing on whether the analyses presented at that meeting are scientifically and technically sound in general and whether they address the concerns raised by the NRC in its first three letter reports. The committee's full statement of task, as developed with your office, is provided in the main body of this report.

The committee reviewed the material presented by the NIH contractors on September 22 and concluded that it cannot endorse as scientifically and technically sound the illustrative analyses presented. These analyses do not, so far, represent a thorough assessment of the public health concerns raised by the committee in its previous reports. The committee understands that the analytical results discussed were incomplete and that work on additional analyses is still ongoing. We hope, therefore, that the comments provided in this letter report will be helpful to you and the Blue Ribbon Panel as you consider how the remainder of the work to be performed is carried out.

[1] The principal operating arm of the National Academy of Sciences and the National Academy of Engineering.
[2] A list of committee members and their biographies is included as Attachment A.

Based on its review of the limited information provided, the committee has a few overarching concerns. First, it appears that the contractor has not yet been responsive to the committee's recommendation that qualitative analyses addressing the three questions[3] raised in our 2008 letter report be prepared first. Quantitative analysis should then be used to supplement the qualitative approach for the pathogens and release scenarios for which there appear to be potentially significant risk and where there are sufficient data to support the analyses. The committee has a related concern about the inputs to the modeling, most importantly the fact that a modified Delphi process was used to gather expert opinions that were then used as a substitute for actual data for modeling. This approach would not have been necessary if the committee's recommendation that qualitative assessments be developed first had been followed. The committee also reiterates the need to include actual data in the models when they are available, for example, data on the speed of secondary transmission of SARS based on published results. Again, the models used must also be transparent, couched in the context of the risk assessment, and include attendant uncertainties.

While the committee commends NIH, Tetra Tech, and its subcontractors for carrying out some illustrative quantitative risk calculations, much work still needs to be done to adequately assess and communicate the risks associated with the NEIDL. Our report offers additional specific comments on the uncertainty analyses used in the modeling; the need to document assumptions; other issues concerning modeling; the need for case studies; and identification of vulnerable and susceptible populations.

This report reflects the consensus of the committee and has been reviewed in accordance with standard NRC procedures. The work was supported by Frances Sharples, Director of the NRC's Board on Life Sciences, Panola Golson of the Board on Environmental Studies and Toxicology, and Kathi Hanna, our professional science writer.

The committee thanks NIH for seeking its input as it works to develop resources for advancing the national capacity to protect and improve health. The committee hopes that its suggestions will be useful in this regard.

Sincerely,

John F. Ahearne, Chair
Committee on Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL

cc: Amy Patterson, M.D.

[3] Risk triplet, as per S. Kaplan and B.J. Garrick. (1981). On the quantitative definition of risk. *Risk Analyses* 1 (1):11-27.

ACKNOWLEDGMENTS

This report has been reviewed in draft form by individuals 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 this 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 for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

John S. Applegate, University of Indiana School of Law, Bloomington, IN
Kenneth I. Berns, University of Florida, Gainesville, FL
David R. Franz, Midwest Research Institute, Frederick, MD
Charles N. Haas, Drexel University, Philadelphia, PA
Stephen Ostroff, Pennsylvania Department of Health, Harrisburg, PA
Frank Speizer, Harvard Medical School, Boston, MA
Catherine Wilhelmsen, U.S. Army Medical Research Institute for Infectious Diseases, Frederick, MD

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 B. Perrin, University of Washington, Seattle, WA. 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 for the final content of this report rests entirely with the authoring committee and the institution.

BACKGROUND AND INTRODUCTION

In 2003, the Boston University Medical Center (BUMC) was awarded a $128 million grant from the National Institutes of Health (NIH) to build one of two national high- and maximum-containment laboratory facilities for pathogen research. The National Emerging Infectious Diseases Laboratories (NEIDL) are meant to support the National Institute of Allergy and Infectious Diseases' biodefense research agenda, conducting research to develop new approaches to treating, preventing, and diagnosing a variety of bacterial and viral diseases. Diseases and pathogens to be studied include viruses (e.g., Ebola, Marburg, dengue fever, Lassa fever, and highly pathogenic influenza) and bacteria (e.g.,*Shigella* and plague) that occur naturally and cause infections or that could be used in deliberate attacks. The facility includes a biosafety level 4 (BSL-4) containment laboratory housed in a 192,000 square foot building. Although the NEIDL BSL-4 laboratory accounts for only 13 percent of the building's total space, it has been the source of virtually all of the community concern surrounding this project. The location of the facility on Albany Street in Boston's South End, which is an environmental justice community, (Boston Region Metropolitan Planning Organization, Journey to 2030; Loh, et al., 2002) has been controversial, and there have been numerous public meetings over the plans for the facility as well as three legal actions that challenge the project. Construction of the laboratory building is now finished although commissioning of the laboratory facilities has not been completed. A remaining issue is whether the BSL-4 component will become operational.

The building, including the BSL-4 laboratory, is part of the BioSquare Phase II project. Under the Massachusetts Environmental Policy Act (MEPA), the Secretary of the Commonwealth of Massachusetts's Executive Office of Environmental Affairs issued a certificate stating that the BioSquare II project required the preparation of an Environmental Impact Report (EIR). Although the Massachusetts Secretary of Environmental Affairs in 2004 found that the final Environmental Impact Report adequately and properly complied with MEPA, this determination was challenged in court. In July 2006 the Superior Court of Massachusetts vacated Massachusetts' certification of the EIR and remanded the matter to the Secretary of Environmental Affairs.

NIH prepared a document, "Draft Supplementary Risk Assessment and Site Suitability Analyses" (DSRASSA), regarding the siting and operation of the NEIDL in response to comments from the federal court presiding over another lawsuit under the National Environmental Policy Act (NEPA) and to supplement NIH's previous assessments of the potential risks posed by the NEIDL at its current location in Boston.

At the request of the State of Massachusetts, in November 2007 the NRC committee authoring the current report released the first in a series of letter reports assessing the DRASSA.[4] The committee's assessment was critical of the DSRASSA, finding that it was not sound and credible, did not adequately identify and thoroughly develop worst-case scenarios, and did not contain the appropriate level of information to compare the risks associated with alternative locations. The report also raised specific concerns about agent selection, scenario development, modeling methodology, environmental justice issues, and risk communication.

In March 2008, NIH established its Blue Ribbon Panel (BRP) to provide scientific and technical advice to the NIH Director through recommendations made to the Advisory Committee

[4] NRC. Technical Input on the National Institutes of Health's Draft Supplemental Risk Assessments and Site Suitability Analyses for the National Emerging Infectious Diseases Laboratory, Boston University: A Letter Report (2007). Available at: http://www.nap.edu/catalog/12073.html.

to the Director. The panel members were charged with providing ongoing, expert input to guide the development of any necessary additional risk assessment analyses. Also in 2008, the same NRC committee reconvened at the request of NIH. The NRC committee has been meeting with the BRP periodically as milestones were reached in the preparation of additional risk assessment materials. The NRC released its second letter report in April 2008.[5] The committee restricted its comments in that report to suggestions based only on its previous review of the DSRASSA and improving the risk assessments presented therein as input to any additional studies that may be needed to assess risk associated with the siting and operation of the NEIDL. As noted in its 2007 report, the committee acknowledged and emphasized the need for biocontainment laboratories, including BSL-4 laboratories. However, the committee's view remained that the selection of sites for high-containment laboratories should be supported by detailed analyses and transparent communication of the available scientific information regarding possible risks.

In its 2008 report, the committee refrained from prescribing specific methods and other details, electing instead to structure its suggestions to the NIH BRP around the following overarching questions that should be addressed in future reports about the risks associated with operating the NEIDL:

- What Could Go Wrong?
  - Release scenarios for infectious agents
  - Agents to consider for risk assessment
- What are the probabilities that these scenarios will occur?
- What would be the consequences if they did occur?

The committee also recommended that NIH make greater use of the accumulated wisdom in the published literature on how to achieve effective risk communication.

In 2009 NIH asked the NRC to convene the committee again to provide input at key milestones in the development of the supplementary risk assessment through a series of letter reports (see full Statement of Task, below). The first milestone for which input from the NRC was requested was the development of plans for the supplemental risk assessment. On March 19, 2010 at a joint meeting of the NIH BRP and the NRC committee, the two contractor groups selected by NIH to complete the supplemental risk assessment—Tetra Tech and its subcontractors from the University of Utah—made presentations on the proposed plans for the supplemental risk assessment. At NIH's request, the NRC committee focused its discussions of the proposed approaches on the following questions:

1. Is the range of agents being studied appropriate?
2. Is the approach to event sequence analysis appropriate?
   - Will the method result in an adequate range of scenarios being considered and selected for analysis?
   - Are the plans for analysis and expression of results appropriate?
3. Is the modeling approach appropriate?
   - Is the approach to initial infection sound?
   - Are the criteria for and selection of models sound?
   - Are the uses of the hybrid branching-compartment models and the extreme values analysis sound?

[5] NRC. Technical Input on Any Additional Studies to Assess Risk Associated with Operation of the National Emerging Infectious Diseases Laboratory, Boston University: A Letter Report (2008). Available at: http://www.nap.edu/catalog/12208.html.

On the basis of this meeting, in April 2010 the NRC committee delivered its third letter report.[6] In that report, the committee noted that it had heard about plans, but not yet results. In general, the NRC committee found the proposed approaches to conducting the risk assessment suitable and well planned. The agents selected for analysis were appropriate and comprehensive, and the expertise available on and to the assessment team seemed strong. NIH and Tetra Tech appeared to recognize data limitations and the need for flexibility in study design. The committee encouraged NIH and Tetra Tech to develop qualitative analyses (an explanation of the safety and risk profile) of all 13 pathogens on the list in a manner that is clear and accessible to the public. The committee also suggested that the qualitative analyses in the body of the assessment be supplemented with results of quantitative modeling planned for five pathogens, with details provided in appendices. Further, the committee encouraged NIH and Tetra Tech to rely on data that are available from existing case studies, public health surveillance of the surrounding communities, and release incidents, not only to support its models but also to provide a complete and understandable picture for the public. The NRC committee again emphasized that the final risk assessment be able to serve as an effective risk communication tool.

Statement of Task for This Letter Report

This report is also based on a meeting between the BRP and the reconvened NRC committee. As with the committee's April 2010 report, the statement of task for this letter report is as follows:

> The NIH will engage the Committee on Technical Input on the NIH's DSRASSA for the Boston University NEIDL at key milestones during the development of a draft supplementary risk assessment. The NRC and the NIH Blue Ribbon Panel (BRP) will meet together in public to discuss the developing draft report. Information contained in the draft risk assessment may include data on agents, models, and scenarios; preliminary modeling results; and quantitative and qualitative assessments. Documents reviewed and discussed at these meetings will be made available to the public. Following each meeting with the BRP, the NRC Committee in closed session will prepare brief letter reports on the preliminary results of the supplementary risk analyses, focusing on whether the analyses are scientifically and technically sound in general and whether they address the public health concerns previously raised by the NRC in its review of the July 2007 DSRASSA. These letter reports will be made available to the public. The committee will also provide written comments on the draft supplementary risk assessment when that document is made available for formal public comment. The Committee will submit its findings in the form of a final letter report that will also be made available to the public.

The NRC committee and the BRP met in person September 22, 2010 to discuss the developing draft risk assessment. Tetra Tech and its subcontractors from the University of Utah again made presentations, this time addressing some early results of quantitative modeling for the supplemental risk assessment. Presentations were made on:

[6] NRC. Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL, Phase 1: A Letter Report (2010). Available at: http://www.nap.edu/openbook.php?record_id=12902&page=2.

- Release event selection and analysis
- Probability of initial infections
- Modeling secondary transmission, and
- Approach to risk characterization

At NIH's request, the NRC committee focused its analysis on the data presented as examples of the technical approaches being used that have produced some preliminary, but still incomplete, results.

COMMITTEE RESPONSE AND FINDINGS

The committee reviewed the material presented by the NIH contractors on September 22 and concluded that at this point in time it cannot endorse the illustrative analyses presented as scientifically and technically sound or likely to lead to a thorough assessment of the public health concerns previously raised by the NRC. The committee understands that the analytical results discussed were incomplete and work on additional analyses was still ongoing. For this reason, the committee had to base its review on the presentations, without documentation of the scientific rationale for the analyses.

Based on the limited information provided, the committee has a few overarching concerns. First, it appears that the contractor has not yet been responsive to the committee's recommendation that qualitative analyses addressing the three questions raised in its 2008 letter report be prepared first and that these qualitative analyses then be supplemented by quantitative analysis through modeling using available data on the agents in question. The results of modeling are only as good as the quality of the modeling inputs, and the problem of limited data should be addressed in narrative, with supporting scientific rationale for its interpretation, as part of a comprehensive qualitative analysis for the 13 pathogens. Instead, NIH and its contractors used a modified Delphi process to gather expert opinions that were then used as a substitute for data for modeling. Circumventing the absence of data with a Delphi process is a tactical error. Parameter values acquired in this way may be misleading without validation (Kaplan, 1992). Had the NRC's previous recommendations been heeded, it should have been clear that the parameter values acquired in this way were unnecessary. When data are not available in the literature, the contractors should turn to relevant case studies and argue by analogy.

In addition, it is important that modeling be used in a context that reflects scientific knowledge and experience. For example, the University of Utah analysts presented an extensive modeling analysis for plume dispersal of aerosolized Rift Valley Fever virus (RVFv). But because RVFv is transmitted primarily by a vector, it is not an appropriate candidate for aerosol dispersal modeling. The committee reiterates the need to include actual data based on published results in the models where possible, for example, for modeling the speed of secondary transmission of SARS. Again, the models must be transparent and couched in the context of the risk assessment and address appropriate uncertainties.

While it is possible that such analyses will be provided in the final assessment, the committee strongly believes that a mid-course correction by Tetra Tech and its subcontractors will be necessary to reach that point. In short, while the committee commends Tetra Tech and its subcontractors for carrying out some extensive illustrative quantitative risk calculations, much work needs to be done before risks are adequately assessed.

In summary, the results presented on September 22 are insufficient for the committee to find that the analyses presented thus far will lead to a scientifically and technically sound risk assessment. The committee had endorsed the approaches presented at the last meeting in its third letter report, but noted that it had not yet seen results. The illustrative results presented to date are not yet sufficiently documented and supported to convince the committee that the contractors are on track to completing a comprehensive assessment of risk for the NEIDL facility.

The committee offers the following more specific comments on: the process used to generate dose-response models and the dose metrics used; the uncertainty analyses used in the modeling; other issues concerning modeling; the need for case studies based on actual data; and the method used for identification of vulnerable and susceptible populations.

Use of a Delphi Process to Generate Dose-Response Relationships

The committee is very concerned about the method by which dose-response assessment—a critical element of risk assessment for prediction of human infection, morbidity, and mortality—is being handled in the contractor analyses. The committee was informed that NIH elected to use a "modified Delphi method" to generate dose response estimates due to the absence of human data for predicting infections. This process involved soliciting opinions on human infective doses (HIDs) from an expert panel of biodefense specialists and laboratory researchers via questionnaires. Opinions were sought on values for HID_{10}, HID_{50}, and HID_{90}, or the levels of inhalation exposure at which 10 percent, 50 percent, and 90 percent of an exposed human population might become infected with aerosolized pathogenic agents, for 13 pathogens. Although the report on the Delphi process was not presented to the committee at the September 22 meeting with the BRP, the committee subsequently asked for and was given a copy of the draft process report. Although NIH did not ask the committee to comment on the Delphi process report, the committee's review of this report raised additional concerns, which are presented in an appendix (Attachment C). Only the major concerns are summarized here.

The scientific basis for the opinions of the experts involved in the process is not clearly explained in the report, especially regarding scaling animal data to humans, translating routes and endpoints, addressing low-dose issues, and other uncertainties. There is no detailed documentation of how the experts arrived at their individual opinions and judgments or of how interaction among them might have modified their opinions and judgments. Rather, the appendices to the Delphi report provide only numerical scores from "voting." The scientific bases for the estimates derived by the experts, including citations to the published literature, case studies of human outbreaks, and knowledge of laboratory-acquired infections (LAIs), should have been integrated into the project team's reports and presentations. The committee does not find convincing the claim that the experts' conclusions regarding human infectivity from pathogen particles (models fitted to three median point estimates from 8 experts for 13 pathogens) "tracked the literature," because the tabulated studies represent an incomplete accounting of the available literature (see Attachment C). To the committee's knowledge, there has been no outside peer review of the results of the Delphi exercise.

The committee is not in a position to conduct a peer review of the risk assessment results presented because documentation was not provided. However, given the limited documentation provided, the committee is unable to endorse the use of its results in the risk assessment. The analysis presented does not appear to reflect sound scientific judgment or robust risk assessment practices.

Uncertainty and Sensitivity Analyses

Good practice in risk assessment requires transparency and the development ofa **sensitivity analysis** that addresses the effects of variances in the model inputs on results. Methods for deriving sensitivity analyses, typically via variations on Monte Carlo simulations, also usually provide a range of results rather than point estimates. Ranges convey the potential variability of the results better than single point estimates do. Good practice also includes the use of qualitative **uncertainty analysis** (NRC, 1994; Morgan and Henrion,1990). This is a frank discussion of the variables that are the least well understood and thus contribute most to the overall scientific uncertainty of the results. Inputs that may be highly variable but based on reliable data with little scientific uncertainty, such as human inhalation volume, contribute largely to the sensitivity analysis. Other input variables, such as pathogen dose-response, may be highly uncertain due to a lack of scientific data as well as variability within and between hosts. An input also may be highly uncertain and have low variability. Input variables of the latter type would have little impact in the sensitivity analyses, but might drive the total uncertainty of the results. The Tetra Tech team discussed the use of Latin Hypercube Sampling (LHS) as their basis for uncertainty analysis, but it was not clear whether these LHS analyses really addressed sensitivity, rather than uncertainty, analysis. The Tetra Tech team should exercise greater care in presenting these aspects of the data used for modeling and assure that both uncertainty and sensitivity analyses are adequately developed.

In addition, the committee is not persuaded that the "uncertainty analysis" provided has much useful content in its current form. As one example already mentioned above, it is inadequate to consider that the uncertainty in the dose-response relationship could be represented as a question of which of the eight Delphi process experts is correct, when another possibility is that none of the curves developed from the three points elicited from each expert provide the true human dose-response curve. Nor is it adequate to state that the results of fitting models to three median point estimates from 8 experts for 13 pathogens "tracked the literature" when the referenced studies represent an incomplete understanding of the available literature.

Incompleteness of the Analyses and Lack of Documentation for Assumptions

The Tetra Tech analyses presented to the committee contain undocumented or poorly documented assumptions. For example, the aerosol release from a centrifuge accident was described as a "10 ml leak from container into rotor, but only a small fraction is aerosolized." How was the judgment made on how much of the 10ml was aerosolized? Is this fraction an important uncertainty? What was the quantity of pathogen contained in the release? No bounding calculation is given, such as the result if all 10 ml are aerosolized. This uncertainty was apparently not a component of the uncertainty analysis described, which is restricted to only a few parameters. While there are many acceptable ways to conduct a valid risk assessment and the choices made by the contractor team may be defensible, provision of the details of the many unspecified assumptions for the calculations behind the numerical results and risk matrices provided on September 22 would greatly improve the committee's understanding of the strengths and limitations of the work conducted.

Risk assessment should provide insight on what events and processes give rise to risk, and then allow the acceptability of the risk—and the potential risk reduction from improved equipment and procedures—to be evaluated (NRC, 1996). Given the lack of cohesive knowledge of the dose-response relationships for the various pathogens in humans and animals, and the two disease transmission examples (RVF and SARS CoV), the presentations may have merit as

illustrating the types of calculations needed for a risk assessment. But the committee is not persuaded that the project team has yet made progress in exploring and documenting the important issues for the NEIDL.

Consideration of the available case studies (such as the SARS case described below) suggests the possibility that transfer of a pathogen outside the laboratory by an infected worker is an important class of risk events. Such transfers can lead to diverse outcomes, for example, no secondary transfer in a recent case of tularemia in Maryland, but transfers producing secondary infections from laboratories studying more highly contagious pathogens. Scenarios for infection outside leading to secondary transmissions should be considered in addition to the centrifuge example, particularly where there are documented case studies of LAIs. As noted above, the degree of documentation of the details—such as for the centrifuge accident and the dose-response relationships for pathogens—is too sparse to be persuasive.

Modeling

The committee continues to believe that the use of branching process models and compartmental models is appropriate, rational and straightforward. The committee was pleased with the progress made with the two branching process models described in the presentation. However, based on what was presented, the committee has serious concerns about the modeling context and, in at least one instance, with the manner in which the models were implemented.

First, as noted above, the committee was disappointed with the extent to which qualitative and quantitative approaches were integrated in the September 22 presentations. To be clear, the committee believes that presenting the modeling results without also describing the natural history of a pathogen, the characteristics of the disease outbreaks with which the pathogen has been associated, and experience with the pathogen in the context of known releases from laboratories diminishes the credibility of these results, which cannot be expected to stand alone without an appropriate context and explication. It would boost confidence in the model if the insights it provides generally match the expectations engendered by field experience. If the insights appear to contradict the expectations of experienced researchers, then the specific circumstances that make such results plausible must be explained. For example, the results of the SARS modeling presented to the committee appear to be counterintuitive, yet no credible explanation was provided of why the risks of secondary infection transmission should be the same for urban, suburban, and rural sites with their significant differences in population density.

On the contrary, the committee notes that this counterintuitive outcome may have much to do with the fact that internal restrictions in the MACCS2 model do not allow modeling of a pathogen release within 100 meters of the building release site. The Tetra Tech team's results "showed" that the concentrations of aerosol at the rural and suburban sites were "two- to four-times higher" than at the urban site due to the increased turbulent mixing of the released puff in the rougher urban topography. Modeling a plume within the first 100 meters of release in an urban zone is admittedly difficult. However, if the puff at exit from the building is assumed to be the same concentration for all locations, the higher population density in the urban location could be associated with higher risk than the suburban and rural sites, which have lower population densities. Thus, it may not be true, as Tetra Tech concluded, that risks are higher in the suburban and rural locations. This 100-meter zone gap in the plume modeling must be more satisfactorily addressed and cannot be ignored as it appeared to have been in the presentations. Perhaps upper bound risk conditions, such as low wind speed, atmospheric stability, and an early morning

inversion where mixing complexities may be minimal and urban canyon channeling a major factor, could be considered.

In recent years, a great deal of research in modeling the near field, less than 100 meter urban zone, has been completed due to societal and government concerns over the potential impacts of release of chemical or biological agents by malevolent or other action. Alternatives to MACCS2 exist that Tetra Tech could consider. Granted, parameters for and methods of handling building downwash, building upwash, urban canyon channeling, building wake turbulence and other factors of the urban topography remain difficult to handle with certainty. These can be an issue in a suburban and rural near field as well. (Some publications that further discuss the problems and approaches to modeling include Belcher, 2005; Pullen, et al., 2005; Olvera and Choudhuri, 2006; Burrows, et al., 2007; Neofytou, et al., 2008; Singh, et al., 2008; and Brixey, et al., 2009.

The committee also has a specific concern with the implementation of the SARS modeling related to the way in which mitigation strategies were represented by an "instantaneous" reduction in the value of the reproduction number. This is not supportable. There are several sources that document gradual decreases in the reproduction number for a range of diseases. In almost all cases, the decline occurs over a period of weeks, not instantaneously. In the case of SARS, the decline in the estimated reproduction number can take between 5 and 25 days even in a hospital environment with an already recognized problem (Cooper. et al., 2009).

Finally, the committee notes that the intensive effort put into plume modeling and the earthquake scenario (stated as the worst case) places a great overemphasis on risk pathways that are not particularly relevant to Rift Valley Fever (primarily transmitted by mosquitoes) and SARS (highly transmissible person-to-person and a major concern for an infected laboratory worker).

Vulnerable Populations

The September 2010 presentations indicated that the Tetra Tech team had identified the vulnerable or sensitive groups as "those 5 years of age or younger, those 65 years of age or older, those with diabetes mellitus, those with HIV/AIDS, and those who are pregnant." The report from the modified Delphi process with the expert panel listed the median percentage increases in vulnerability to disease and death among these five groups. These percentage increases were then used to calculate the increased risk of infection at each site (if any) based on the percentage of population falling into these groups. Although the committee believes that the contractors' approach and its presentations at the September meeting contributed to a meaningful discussion of the issues surrounding vulnerability and sensitive subpopulations, to meet the risk assessment goals that this committee set out in its previous reports, the contractors should recast their vulnerability analysis and shift direction, as explained below.

Refining, Re-evaluating and Making Key Assumptions Transparent

The committee recommends that the contractors consider re-evaluating and refining several of their key assumptions regarding vulnerable and sensitive subpopulations. First, it is not clear how these categories of vulnerable groups were determined, but the committee gathers that they were presented to the expert group in the Delphi exercise, not developed as a result of that exercise. Appendix A, Part C of the Delphi process report states that "the groups have been dictated in part by the level of data available for the sites being evaluated." Because this report was made available after the September 22 presentation, the committee did not have the

opportunity to discuss this statement, or the vulnerability group criteria, with the Tetra Tech team. Based solely on its reading of this language, it appears that the published literature and available data were the key criteria for selection of vulnerable groups. As discussed below, the committee presents a different approach for consideration. Second, the contractors used these vulnerability categories only to estimate additional infection rates, though the experts addressed percentage increases in vulnerability to disease and death. The committee believes that the contractors should address both increased risk for mortality and more serious health outcomes (severe morbidity). This issue was not addressed in the presentations even though the Delphi report specifically asked experts to assign probabilities for both increased disease (morbidity) and mortality. Third, the modeling carried out by the Tetra Tech team assumed that no member of groups at risk for primary infection was a member of a vulnerable subpopulation. This assumption does not seem realistic. For modeling purposes, it would seem more prudent to assume that some proportion of individuals at risk for primary infection could also be a member of a vulnerable group (e.g., diabetics).

Refining and Re-evaluating the Concept of Vulnerable and Sensitive Subpopulations

As explained previously, the committee cannot comment in detail about the methodology used to determine the vulnerable categories used by the Tetra Tech team. If this methodology were made transparent, the committee would be in a better position to offer a critique and suggestions for next steps. Nevertheless, based on the September presentations, the committee believes that the Tetra Tech team could make some improvements in determining these categories. While it might be possible to include previously gathered data into this new evaluation, a different methodology will better serve the risk assessment and the decision makers who will use it.

EPA's National Environmental Justice Advisory Committee (NEJAC) set out a conceptual model that the committee believes is useful and should be considered by the Tetra Tech team (NEJAC, 2004). The model defines several key concepts, such as stressors, and conceives vulnerability broadly. More particularly, EPA's NEJAC defines four important characteristics of vulnerable populations:

1. More susceptible or sensitive to disease outcomes
2. Differentially exposed to environmental conditions that could render these populations more vulnerable
3. Differentially prepared to address deleterious conditions, such as exposures to infectious diseases, and
4. Differential responses to the same level of infection or exposure (as non-vulnerable populations) that may worsen response.

The South Boston and Roxbury neighborhoods that are potentially affected by the NEIDL facility have been identified as environmental justice communities and a vulnerable population analysis should take that into consideration. These communities suffer from higher rates of several chronic diseases, including asthma, which is not one of the higher risk factors presented, and have a much greater population density (see discussion below on dispersal modeling). The rural and suburban communities to which they are being compared are not environmental justice communities, to the best of the committee's knowledge.

In recasting its vulnerability analysis, the committee urges the Tetra Tech team consider the following steps:

- Develop a robust methodology for determining categories of sensitive or vulnerable individuals. In doing so, the committee recommends that Tetra Tech adopt the EPA NEJAC conceptual framework as a starting point, and consult with community leaders, public health professionals familiar with the South Boston and Roxbury areas, and review the published public health literature and health surveillance data, if available.
- Evaluate not only increased infectivity or morbidity, but also increased disease severity for vulnerable and sensitive subpopulations. This analysis should include endpoints such as mortality and, if possible, those that represent predicted differential morbidity outcomes.
- Model primary infection assuming that some of the individuals at risk for such infection might also be members of vulnerable groups.

Use of Case Studies

In its April 20, 2010 letter report, the committee made a specific recommendation in the modeling subsection that "modeling should be augmented by case studies based on actual occurrences of laboratory or natural infections." The committee believes that case studies can be used not only to provide information on how and whether LAIs may or may not be transmitted to the general population by infected workers. They may also provide ground truth examples for how potential time of exposure to a pathogen compares to time of recognition of an LAI, secondary transmission of the disease, and the effectiveness of treatment.

There are a number of well-documented accounts of recent LAIs that could be used in the development of brief case studies to illustrate more clearly the effect of infected laboratory workers on community health. Examples include, but are not limited to, infection with *Brucella spp*, SARS virus (see Box as an example), *Francisella tularensis*, and *Burkholderia mallei*. In addition, case studies describing naturally occurring illness can be developed for those agents potentially studied at NEIDL for which well documented or recent LAI have not been reported. A few examples include infection with *Yersina pestis* (tourists in New York), Monkey pox virus (contracted from exotic pets), *Bacillus anthracis* (contaminated drum hides), Marburg virus (a tourist who visited Uganda), and U.S. experience involving the recent H1N1 influenza virus pandemic. The committee is not advocating that these specific examples be developed as case studies, but believes that available information on a variety of the agents to be studied at the NEIDL could be used to provide context and a basis for reality to the qualitative aspect of the risk posed to the local community by an infected laboratory worker. A 2010 NRC report, *Evaluation of the Health and Safety Risks of the New USAMRIID High-Containment Facilities at Fort Detrick, Maryland,* provides a list of laboratory incidents that have occurred at USAMRIID's laboratories that might provide useful examples from which to develop case studies. In the box below, the committee provides an example to illustrate what it means.

Sample Case Study: SARS/CoV

In China, SARS/CoV was grown in a BSL-3 laboratory by a worker who apparently had worn inappropriate personal protective equipment (PPE) and then treated the sample to inactivate the virus before removing it to a BSL-1 laboratory for further work on the open bench. The worker failed to verify the complete inactivation of the virus and subsequently became ill and was admitted to a fever hospital. The laboratory was not notified of this development and the worker later returned to the laboratory. A second worker who handled the "inactivated" sample also became ill. A graduate student who observed the laboratory procedure later traveled by train to

her home several hundred miles away. After returning to the laboratory she became ill and once again traveled to her home by train where her mother, a physician, admitted her to a hospital and treated her. The student was asked if she worked with SARS/CoV (she said no because her research involved another virus). It was not until the mother became ill and died that SARS/CoV was identified. Other laboratory workers also became ill and other hospital personnel died. This case study illustrates several important points: people make mistakes (improper PPE); not everyone follows procedures (failure to test sample for inactivity); people may die if not properly diagnosed and treated.

Metrics

The committee believes that Tetra Tech should carefully consider what might be the appropriate metric(s) when evaluating the transmission of pathogens in heterogeneous human populations. The metric presented to the committee was the probability that a release would not lead to secondary transmission (probability of > 0 transmissions). This probability arises naturally and easily out of multiple stochastic simulations—and may be of interest to a policymaker concerned with the health and well being of the population as a whole—but it will be of no interest to those groups at particular risk of infection. Such at-risk groups will want to know what might happen to them should an introduction in fact lead to a secondary transmission.

SUMMARY

NIH and its contractors have not yet been responsive to the committee's recommendation for tiered qualitative and quantitative analyses. The committee strongly recommended that qualitative analyses address the three questions raised in its 2008 letter report —What could go wrong? What are the probabilities? What are the consequences?— be prepared first for all 13 agents of concern using available data and case studies to scope or bound the problem broadly. The committee intended that this first tier of qualitative analyses would then be supplemented by second tier quantitative analysis for a subset of agents as necessary for decision making.

However, instead of beginning with a first tier qualitative analysis of both direct and indirect scientific evidence to bound the analysis for the 13 pathogens, a modified Delphi process was used to gather expert opinions on multiple unknown parameters. The results were then used as a substitute for data for all 13 agents. The median opinions for three infectious doses were fitted to empirical models intended to predict human infectivity for exposures generated by plume/puff models that also relied on opinions for influential parameters. Circumventing the absence of data with a Delphi process and then conducting modeling based on opinions was a tactical error. The committee considers the approach flawed in large measure because reliance on opinions for quantitative second tier modeling was unnecessary In addition, the approach is problematic because the elicited opinions about possible parameter values, and the models fitted to them, may be incorrect and misleading without validation.

To expedite completion of a robust risk assessment, the committee strongly urges a mid-course correction to the use of tiered qualitative and quantitative analyses. The first tier should use narrative descriptions based on case studies and actual data reporting, with supporting scientific rationales provided for interpretation. Then, a more targeted second tier quantitative analysis should be developed where the existence of quantitative data allows. The quantitative analyses should reflect what is known from case studies and real world experience about transmission modes and other critical parameters.

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Attachments:
A Committee Membership and Biographies
B September 22, 2010, Open Session Public Agenda
C Appendix: Comments on the report "Expert Consultation on Infectiousness of Organisms Studied in the NEIDL Risk Assessment"

Attachment A

Committee on Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL

JOHN AHEARNE *(Chair)*, The Scientific Research Society, Research Triangle Park, NC
THOMAS ARMSTRONG, TWA8HR Occupational Hygiene Consulting, LLC, Branchburg, NJ
GERARDO CHOWELL, Arizona State University, Tempe, AZ
MARGARET COLEMAN, Consultant, Cicero, NY
GIGI KWIK GRONVALL, University of Pittsburgh, Baltimore, MD
ERIC HARVILL, Pennsylvania State University, University Park, PA
BARBARA JOHNSON, Barbara Johnson & Associates, LLC, Herndon, VA
PAUL LOCKE, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
WARNER NORTH, NorthWorks, Inc., Belmont, CA
JONATHAN RICHMOND, Jonathan Richmond & Associates, Southport, NC
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Staff

FRANCES SHARPLES, Project Director
KATHI E. HANNA, Consultant Writer
PANOLA GOLSON, Program Associate

Committee Biographies

John Ahearne (chair) is Executive Director Emeritus of Sigma Xi, the Scientific Research Society, and Emeritus Director of the Sigma Xi Ethics Program. Prior to working at Sigma Xi, Dr. Ahearne served as Vice President and Senior Fellow at Resources for the Future and as Commissioner and Chair of the U.S. Nuclear Regulatory Commission. He worked in the White House Energy Office and as Deputy Assistant Secretary of Energy. He also worked on weapons systems analysis, force structure, and personnel policy as Deputy and Principal Deputy Assistant Secretary of Defense. Serving in the U.S. Air Force (USAF), he worked on nuclear weapons effects and taught at the USAF Academy. Dr. Ahearne's research interests include risk analysis, risk communication, energy analysis, reactor safety, radioactive waste, nuclear weapons, materials disposition, science policy, and environmental management. He was elected to the National Academy of Engineering in 1996 for his leadership in energy policy and the safety and regulation of nuclear power. Dr. Ahearne has served on many NRC Committees in the past twenty years, and has chaired a number of these, including the current Committee on Evaluation

of Quantification of Margins and Uncertainty Methodology Applied to the Certification of the Nation's Nuclear Weapons Stockpile and the Committee on the Internationalization of the Civil Nuclear Fuel Cycle. He is a Fellow of the American Academy of Arts and Sciences, the American Physical Society, the Society for Risk Analysis, and the AAAS. In 1966, Dr. Ahearne earned his Ph.D. in Physics from Princeton University.

Thomas W. Armstrong retired in 2008 from his position as Senior Scientific Associate in the Exposure Sciences Section of ExxonMobil Biomedical Sciences, Inc., where he worked since 1989. Dr. Armstrong also worked with the University of Colorado Health Sciences Center as the lead investigator on exposure assessment for epidemiological investigations of potentially benzene-related or other occupational exposure-related hematopoietic diseases in Shanghai, China. Dr. Armstrong also spent nine years working for the Linde Group, as both the manager of loss control in the gases division and as a manager of safety and industrial hygiene. Dr. Armstrong conducted research on quantitative risk assessment models for inhalation exposure to Legionella, and remains professionally active on that topic. He has recently contributed to publications on mathematical models to estimate exposures to hazardous materials, and methods for exposure reconstruction. He was a member of the Society for Risk Analysis and remains an active member of the American Industrial Hygiene Association. The American Board of Industrial Hygiene certifies him as an Industrial Hygienist. Dr. Armstrong has an M.S. in Environmental Health and a Ph.D. in Environmental Engineering from Drexel University.

Gerardo Chowell is an Assistant Professor at the School of Human Evolution and Social Change at Arizona State University. Prior to joining ASU, Dr. Chowell was a Director's postdoctoral fellow with the Mathematical Modeling and Analysis group (Theoretical Division) at the Los Alamos National Laboratory. He performs mathematical modeling of emergent and re-emergent infectious diseases (including SARS, influenza, Ebola, and Foot-and-Mouth Disease) with an emphasis in quantifying the effects of public health interventions. His research interests include agent-based modeling, model validation, and social network analysis. Dr. Chowell received his Ph.D. in Biometry from Cornell University and his engineering degree in telematics from the Universidad de Colima, Mexico.

Margaret E. Coleman is a medical microbiologist, risk analyst, and sole proprietor of Coleman Scientific Consulting. She serves as Councilor of Upstate NY Society for Risk Analysis and various leadership roles, including her appointment to the Editorial Board for the journal *Risk Analysis.* Also an active member of the American Society for Microbiology (ASM), she recently contributed an article to ASM's *Microbe* (*Microbial Risk Assessment Scenarios, Causality, and Uncertainty*). Ms. Coleman contributes to peer review processes for several journals, including SRA's journal *Risk Analysis.* She was selected as an expert in European Food Safety Authority database, as an expert reviewer for two NRC Reports (*Reopening Public Facilities After a Biological Attack; Evaluation of the Health and Safety Risks of the New USAMRIID High Containment Facilities),* and as a committee member on the *Review of Testing and Evaluation Methodology for Biological Point Detectors*. Ms. Coleman contributed extensively to the published literature on quantitative microbial risk assessment for infectious agents in air, food, and water. She recently developed freelance work on health risks from dermal exposure to *Bacillus* spores for a new client. Ms. Coleman earned her B.S. degree from SUNY College of

Environmental Science and Forestry at Syracuse and M.S. degrees from Utah State University and the University of Georgia in Biology/Biochemistry and Medical Microbiology.

Gigi Kwik Gronvall is a Senior Associate at the Center for Biosecurity of University of Pittsburgh Medical Center (UPMC) and Assistant Professor of Medicine at the University of Pittsburgh. An immunologist by training, Dr. Gronvall's work addresses how scientists can diminish the threat of biological weapons and how they can contribute to an effective response against a biological weapon or a natural epidemic. She is a term member of the Council on Foreign Relations and also serves on the American Association for the Advancement of Science (AAAS) Committee on Scientific Freedom and Responsibility. Dr. Gronvall is a founding member of the Center for Biosecurity of UPMC and, prior to joining the faculty in 2003, she worked at the Johns Hopkins University Center for Civilian Biodefense Strategies. From 2000-2001 she was a National Research Council Postdoctoral Associate at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland. Dr. Gronvall earned a Ph.D. from Johns Hopkins University for her work on T-cell receptor/MHC I interactions.

Eric Harvill is an Associate Professor of Microbiology and Infectious Diseases at the Pennsylvania State University. His primary research interest is in the interactions between bacterial pathogens and the host immune system, and his group investigates both bacterial virulence factors and host immune functions at the molecular level using the tools of bacterial genetics and mouse molecular immunology. These studies investigate the effects these molecular-level activities may have on the population-level behavior of infectious diseases. Dr. Harvill has served on several NRC committees, including the Committee on Methodological Improvements to the Department of Homeland Security's Biological Agent Risk Analysis. He has reviewed for more than 20 scientific journals and serves on the Editorial Board for *Infection and Immunity*. Dr. Harvill has reviewed proposals for six different National Institutes of Health study sections, the U.S. Department of Agriculture and multiple international funding organizations. He has organized international and local meetings and chaired sessions at annual meetings of both the American Association of Immunologists and the American Society for Microbiology. He earned his Ph.D. at the University of California, Los Angeles.

Barbara Johnson has over 15 years of experience in the U.S. Government in the area of biosafety, biocontainment and biosecurity, and currently owns the consulting company Barbara Johnson & Associates, LLC. Dr. Johnson has managed the design, construction and commissioning of a BSL-3 Aerosol Pathogen Test Facility, and she launched the U.S. Government's first chemical and biological counterterrorism training facility. Research areas include biological risk assessment and mitigation, testing the efficiency of respiratory protective devices, and testing novel decontamination methods against biological threat agents. In the private sector she pioneered the development of the first joint biosafety and biosecurity programs between the United States and institutes in the former Soviet Union, and founded and directed a Center for Biosecurity in association with this work. She has served as the President of the American Biological Safety Association, and is the Co-editor of the journal Applied Biosafety.

Paul A. Locke is an Associate Professor in the Department of Environmental Health Sciences (EHS) at the Johns Hopkins Bloomberg School of Public Health. He is a public health scientist

and attorney with expertise in risk assessment and risk management, radiation protection law and policy, and alternatives to animals in biomedical testing. Dr. Locke is a member of the Board of Directors of the National Council on Radiation Protection and Measurements (NCRP) and chaired the NCRP's 2010 annual meeting program committee. From 2004 until 2009 he was a member of the NRC Nuclear and Radiation Study Board, and has participated on two NRC Committees that evaluated the risks associated with the disposal of high-level radioactive waste. Dr. Locke has received several awards, including the Yale School of Public Health Alumni Service Award, and the American Public Health Association Environment Section Distinguished Service Award. He holds an M.P.H. from Yale University School of Medicine, a J.D. from Vanderbilt University School of Law, and a Dr.P.H .from the Johns Hopkins Bloomberg School of Public Health. He directs the EHS doctoral program in Public Health.

Warner North is President of NorthWorks, Inc., a consulting firm in Belmont, California. Dr. North is also a consulting professor in the Department of Management Science and Engineering at Stanford University. Over the past 40 years, Dr. North has carried out applications of decision analysis and risk analysis for electric utilities in the United States and Mexico for petroleum and chemical industries, and for government agencies with responsibility for energy and environmental protection. He has served as a member and consultant to the Science Advisory Board of the Environmental Protection Agency since 1978, and as a presidentially appointed member of the U.S. Nuclear Waste Technical Review Board. Dr. North has served as a member of the NRC's Panel on Public Participation in Environmental Assessment and Decision Making and on numerous NRC Boards and Committees, twice as Committee Chair. Dr. North is a past president of the International Society for Risk Analysis, a recipient of the Frank P. Ramsey Medal from the Decision Analysis Society for lifetime contributions to the field of decision analysis, and a recipient of the Outstanding Risk Practitioner Award from the Society for Risk Analysis.

Jonathan 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 ten years as a research virologist, and has been involved in the field of biosafety for the past 25 years. He has authored many scientific publications in microbiology, 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.

Gary Smith is Chief of the Section of Epidemiology and Public Health in the School of Veterinary Medicine at University of Pennsylvania. He has a secondary appointment in the Department of Biostatistics and Epidemiology at the University of Pennsylvania's School of Medicine and is an Associate Scholar in the Center for Clinical Epidemiology and Biostatistics. He is also an affiliated faculty member of Penn's Institute for Strategic Threat Analysis and Response. His research deals with the epidemiology and population dynamics of infectious disease in humans as well as wild and domestic animal species. He has extensive experience of mathematical modeling in the context of infectious and parasitic disease control strategies (including the evolution of drug resistance) and has published case-control studies on a range of

infectious diseases of animals and humans. Dr. Smith served on an FAO/WHO Expert Committee on the implementation of farm models in the developing world; he served on the Pennsylvania Food Quality Assurance Committee, and he was a member of a European Union Expert Committee on Bovine Spongiform Encephalopathy risk. He has served on the editorial boards of *Parasitology Today, The International Journal of Parasitology*, *The Veterinary Quarterly*, and *Frontiers in Ecology and the Environment.* Dr. Smith earned Bachelors degrees in Zoology and Education from the Universities of Oxford and Cambridge respectively and a D.Phil. in Ecology from the University of York.

Attachment B

NIH Blue Ribbon Panel to Advise on the Risk Assessment of the National Emerging Infectious Diseases Laboratories at Boston University Medical Center

September 22, 2010

Hyatt Regency Bethesda
7400 Wisconsin Avenue
Bethesda, Maryland 20814

AGENDA

8:45 AM **Welcome and Purpose of Today's Meeting**
Adel Mahmoud, M.D., Ph.D.
Chair, NIH Blue Ribbon Panel
Professor, Department of Molecular Biology, Princeton University

8:55 AM **Opening Remarks**
John F. Ahearne, Ph.D., Committee Chair, National Research Council

9:00 AM **Roundtable Introduction of Blue Ribbon Panel and National Research Council Members**

9:10 AM **Introduction and Overview of Today's Presentations**
Frank Gallegos, Risk Assessment Project Manager, Tetra Tech

9:20 AM **Release Event Selection and Analysis**
Ken Bulmahn, Tetra Tech Risk Assessment Team Lead

10:00 AM **Discussion**

10:30 AM **Break**

10:45 AM **Probability of Initial Infections**
Adi Gundlapalli, M.D., Ph.D., M.S., Assistant Professor, Departments of Internal Medicine, Pathology and Biomedical Informatics, University of Utah School of Medicine

11:25 AM **Discussion**

11:45 PM **Break**

12:00 PM **Modeling Secondary Transmission**
Damon Toth, Ph.D., Research Assistant Professor, Department of Mathematics, University of Utah

12:40 PM **Discussion**

1:10PM **Approach to Risk Characterization**
Adi Gundlapalli, M.D., Ph.D., M.S.

1:30 PM **General Discussion**

2:30 PM **Public Comment**

2:50 PM **Wrap Up**

3:00 PM **Adjourn**

ATTACHMENT C

Comments on the Report "Expert Consultation on Infectiousness of Organisms Studied in the NEIDL Risk Assessment"

The committee was informed that NIH elected to use a "modified Delphi method" to generate dose response estimates due to the absence of human data for predicting infections. This process involved soliciting opinions on human infective doses (HIDs) from an expert panel of biodefense specialists and laboratory researchers via questionnaires. Opinions were sought on values for HID_{10}, HID_{50}, and HID_{90}, or the levels of inhalation exposure at which 10 percent, 50 percent, and 90 percent of an exposed human population might become infected with aerosolized pathogenic agents, for 13 pathogens. Although the report on the Delphi process was not presented to the committee at the September 22 meeting with the BRP, the committee subsequently asked for and was given a copy of the draft process report (9 July, 2010 draft by Sam Bozzette). This appendix elaborates on the committee's concerns with this process.

One major concern is about a lack of a cohesive scientific rationale in the report for "votes" on parameter values, especially those for the human infectivity point estimates, but also for the other elicited parameters. The report introduces a presumption that "extrapolation from animal experiments is risky because of interspecies differences" and concludes that the elicited opinions of experts converged and "differed from fragmentary human, animal, and laboratory data in reasonable ways." No scientific support is presented for this conclusion.

The NRC committee was told that there were "three rounds of voting" by the experts for all 13 pathogens, and that "individual expert curves" were used for the uncertainty analysis. Essentially no further information was contained in the presentation on this "Modified Delphi method" or how the values from the different experts were used in the analyses.

The copy of the report and its appendices obtained by the committee included the questionnaire used to elicit the "informed iterative confidential voting" by the members of the panel. Rounds of voting were repeated until an unspecified definition of "consensus" was met or for a specified number of cycles (3). Most of the work was done independently by the experts who were provided instructions, background materials (presumably appendix tables prepared by Tetra Tech and lists of abstracts and references from Tetra Tech's literature search), and an electronic questionnaire form to record the first round votes on human infectivity, half-life, and percentage increases in vulnerability for more susceptible human populations. On May 18, 2010, 6 of the 8 experts convened for a day to discuss results of the first round votes and participated in the second round of voting, but no transcript or summary of the discussions among the experts was provided. Apparently, consensus was not reached at this stage of the modified Delphi process, and a third round of votes was conducted later. The only references cited in the report are a Rand study on Delphi process (Dalkey et al., 1962) and two studies on consensus methods (Fink et al., 1984; Jones and Hunter, 1995).

The central idea of a Delphi process is to solicit information (data, evidence, judgment, opinion) from experts separately and then consider anonymous feedback from the other experts that is then used to revise the information initially provided. Regardless of the details of the approach, a Delphi method is necessarily focused on expert judgments on complex and uncertain quantities. Kaplan (1992) recommends eliciting the "evidence" from experts, not their opinions of point estimates for unknown parameters, to build a consensus body of evidence for use in risk analysis. In addition, Morgan and Henrion (1990) discuss combining judgments from experts and

the Delphi process in this context (pages 164-169). Two points raised by Morgan and Henrion (1990) merit consideration by NIH and its consultants: 1) elicited scientific judgment is not a substitute for proper scientific research; and 2) strict quality control of the process is needed.

Appendix Table 1.A of the report provides a summary of a small portion of the human and animal literature. However, the author does not distinguish clinical data from opinions or simulation results (judgments at best) in this table. For example, no inhaled doses are known for any human inhalation anthrax cases to date, yet three papers are cited for opinions or judgments about **possible** human infective doses. The most relevant studies for risk assessment in non-human primates and rabbits (recent USAMRIID) are not included in the table. Further, only four studies, two each from human and non-human primates, were included in Table 1.A for *Franscisella tularensis* rather than citing the extensive knowledge base for tularemia dose-response relationships for human and non-human primates (8 human infectivity studies; 11 non-human studies for dose-dependencies, including asymptomatic, mild, moderate, severe, and fatal tularemia). The report does not cite historical and recent evidence for laboratory-associated tularemia infections or natural outbreaks of pulmonary tularemia that merit consideration for risk assessment.

The value of the elicited results for predicting human effects is highly uncertain. The metric for eliciting human infectious doses for aerosolized particles including pathogens appears purely hypothetical, and not based on valid scientific studies that measured this parameter. A recent illustrative study with norovirus reported an average number of virions per particle of nearly 400 (Teunis et al., 2009), but the nature and impact of clumping on variability and uncertainty in dose-response relationships was not addressed in the Delphi process. Further, the value of eliciting human infectivity for airborne infectious particles is questionable for pathogens with arthropod vectors as the predominant route of infection. Similarly, the elicited parameter for potentially more vulnerable populations appears purely hypothetical rather than arising from a valid scientific study that corrects for dose.

The phrasing of the elicited parameter (median increase in vulnerability of 5 human groups (young [undefined], older [undefined], diabetes, HIV, pregnancy) that might be more susceptible, in general, to infections of unspecified bacteria and unspecified viruses) is too vague to merit inclusion in the analysis for these 13 biothreat agents. Existing scientific data for normal and more susceptible animals are inconsistent with the magnitude of susceptibility elicited by the expert panel. The maximum elicited parameter for increased vulnerability (30 percent) is dwarfed by actual variability in ID_{30} measured in murine populations, which shifted 5 orders of magnitude for salmonellosis infection (Bohnhoff et al., 1964). Thus, it appears that the modified Delphi process elicited "opinions" that are quite hypothetical, rather than judgments based on data. It is unclear how the experts, individually and collectively, used the background information provided, or expanded the body of evidence to form opinions about human infectivity and other unknown parameters in the process.

It is also unclear how the panel used the background information that included multiple host species and multiple routes of infection, including arthropod-borne vectors. The data on Rift Valley Fever (Table 1.A of the report) lists two experiments involving inoculation in rhesus monkeys and in rats. It states that some rats become infected asymptomatically. This disease may be spread by insects such as mosquitoes, as well as by direct contact, but precise data are scarce. How did the experts on the panel use the available data? How was a dose-response for aerosol exposure for droplets containing RVF virus particles developed? How did the experts extrapolate from data in monkeys and rats to the probability of infection in a human? What assumptions

were made about the number of virions in an aerosol droplet, and how many droplets inhaled were needed for infection, especially at a low concentration of such droplets in the air? Did each expert make an assessment for each number solicited in the questionnaire? Were opinions from panel members with specific expertise weighted differently than panel members with less expertise? For example, it is unclear if the feedback and discussion session considered specific expertise of the panel member whose study of the outbreak in Kenya of Rift Valley Fever was recently published, or if this expert's elicited parameters were weighted differently than those from experts without direct experience.

Additional References for Appendix

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