Center for Advancing Microbial Risk Assessment
Year-2 Annual Report

Submitted to

Ms. Angela Page
National Center for Environmental Research
U.S. Environmental Protection Agency (EPA)
1025 F. Street, NW, Room 3500
Washington, D.C. 20004

Dr. Irwin Baumel
U.S. Environmental Protection Agency (EPA)

And

Dr. Matthew Clark
Department of Homeland Security (DHS)
Washington DC

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Joan B. Rose[1], Charles N. Haas[2], and Tomoyuki Shibata[1]
[1]Department of Fisheries and Wildlife, Michigan State University
13 Natural Resources, East Lansing, MI 48824
[2]Department of Civil, Architectural & Environmental Engineering,
Drexel University, Philadelphia, PA 19104

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Summary of Accomplishments Directors Report
Co-Directors: Joan Rose, Michigan Sate University and Charles Haas, Drexel University

The Center for Advancing Microbial Risk Assessment (CAMRA) was established on September 1, 2005. The following is a summary of administrative accomplishments during Year 2 (September 2006 – September 2007). There has been no change of PIs. In addition to the 14 PIs, 8 postdoctoral fellows and 14 graduate students contributed to the CAMRA's Year-2 accomplishments. The objectives of CAMRA's Projects I - V have not changed as stated in the original proposal.

Directors have facilitated the PI's research projects and interactions. Dr. Rose traveled to visit with CAMRA PIs, and Govt scientists to address research progress and needs. The Science Advisory Committee (SAC) members for CAMRA were finalized and include: Dr Rebecca Parkin at George Washington University, Dr. Thomas Burke at John Hopkins University, Dr. Suresh Pillai at Texas A&M University, Dr. Gertjan Medema at Kiwa Water Research, the Netherlands and Dr. Stephen Morse of the CDC. Telephone conferences were run four times with all principal investigators (PIs) and many times among individual projects. The All PI organizational meeting (which included all PIs, the post-doctoral scientists and PhD students, SAC and sponsors) was held at Carnegie Mellon University Feb. 28-March 1, 2006.

A total of 12 peer reviewed papers were published and 34 presentations were given in national and international conferences by the CAMRA investigators. The Knowledge Repository (KR) system has been used to capture key literature, projects in progress and completed work. The ultimate goal of KR is to create data and knowledge warehouse. To date, a total of 70 LUs have been approved, 38 LUs have been completed (results and findings included) and 126 LUs are currently in progress. All data obtained were assured based on the CAMRA Quality Management Plan, via the KM assurance team under Project V. The Quality Management Plan is currently under revision. Ms. Rebecca Ives who is a new Quality Assurance Officer (QAO) at Michigan State University completed her visits to PIs for auditing their quality assurance protocols (separate report available)

CAMRA communicated outside of the PIs, though lectures and QMRA workshops. Dr. Rose gave lectures on microbial risk assessment at seven universities. CAMRA organized three quantitative microbial risk assessment (QMRA) workshops. 1-day QMRA workshops were held at American Society for Microbiology (ASM) General Meeting in Toronto, Canada on May 21, 2007 and International Water Association (IWA) Health Related Water Microbiology (HRWM) Symposium in Tokyo, Japan on September 9, 2007. There were 26 participants at the Toronto workshop and 30 participants at the Tokyo workshop. The 2nd QMRA Summer Institute was held at Michigan State University (MSU), East Lansing, MI from August 19 to 23, 2007. The summer institute received 3.4 continuous education units (CEUs) from MSU. There were 28 international participants included people from all over the States, Canada, Chile, Netherlands, and Spain. CAMRA received additional funds from Battelle ($25,000) that supported many participants' travel expenses.

Future activities will include an all PI meeting in April, 2008 in Washington DC followed by an EPA/CAMRA conference. A one-day QMRA workshop will be held in Boston on May 31 or June 1, 2008, which has been requested by the American Society for Microbiology (ASM) and a pre-statistics and computer exercise course will be held on August 9 and 10, 2008 at Michigan State University followed by 3rd QMRA Summer Institute from August 11 to 15, 2008.

Key **outputs** and **outcomes** from the Projects I to V are given in following section. PI specific reports are also available in the appendices.

Project I: Exposure, Detection, Fate and Transportation of Agents

PIs: Charles P. Gerba[1], Chris Choi[1], Ian Pepper[1], Syed Hashsham[2], Paul Keim[3], Mark Nicas[4], and William Nazaroff[4]; [1]University of Arizona, [2]Michigan State University, [3]Northern Arizona University, [4]University of California, Berkley

The primary accomplishments in Project I include 1) normalization of decay rates of selected category A agents based on literature reviews, 2) evaluation of virus recovery methods (swab, wipe, and vortexing) from fomites, 3) compiling of instrumental and environmental (water, air, and soil) detection limits for *Bacillus anthracis*, 4) Genotoxicity assessment of quantum dots using Comet assay, 5) selection of the potential surrogates for experimental validation as the best surrogate for *B. anthracis*, 6) identification of the best methods for preparing spores for use in the fate and transport experiments, 7) examination of water distribution system. i) new dispersion coefficients for viruses, ii) evaluation of the perfect mixing assumption in water quality models dispersion patters, iii) development of pattern recognition and axial dispersion artificial neural network, & complex network modeling prediction using water quality models and artificial neural network. 8) The Markov chain model for transport and fate of gas-phase contaminants was extended to particles and analysis showed that a three-dimensional air velocity vector can be posed at each room position at each moment in time.

The publication of normalized decay rates for viruses on fomites allows for the prediction of the survival agents of concern on common indoor fomites. This can be used in models to assess the risk of infection to first responders or other exposed individuals after the release of an agent of concern in buildings. Knowledge of the instrument and environmental detection limit of various available methods is key to the quantification of risk. Availability of surrogates that mimic transport and dispersion of pathogens without the associated harmful health effects improves the ability to minimize risk. The spore purification method provides a standard procedure that is fairly consistent and easy to perform. Findings at Water Village will impact a wide variety of network analyses including prediction of disinfectant residuals, optimal locations for water quality sensors, prediction models for early warning systems, numerical schemes for inverse source identification, and quantitative risk assessment. The Markov chain model for transport and fate of gas-phase contaminants was extended to particles. Gravitational settling was modeled by a first-order rate dependent on particle aerodynamic diameter, and deposition was modeled based on published algorithms for deposition velocity. The model accounts for particle transport via advective flow, turbulent diffusion and gravitational settling, and particle loss from room air by deposition onto the floor and other room surfaces (e.g., walls, ceiling) and by the room exhaust airflow. A particle-size dependent function for the rate of deposition onto walls and the ceiling was derived from measurement data.

In Year-3, Project I will 1) develop decay rates of Picinde virus, yellow fever virus and two other viruses to be selected on fomites and in drinking water, 2) complete laboratory research of on the decay rates of surrogates and agents of concern on fomites under a variety of conditions for use in predictive models, 3) evaluate detection limit for BACs and surrogates, e.g. *Bacillus thuringiensis* and P22 using qPCR and Plaque Assay, 4) continue experiments that will provide parameters for fate and transport models (*i.e.* decay rates for *B. anthracis* spores on several mediums (*i.e.* fomites, water, buffer, soil etc.), 5) continue experimental comparison of several possible *B. anthracis* surrogates to be compared with *B. anthracis* Ames (a virulent strain) with the purpose of validating a surrogate for use in fate and transport experiments, 6) assess the use of coliphages *E. coli* and a bacillus spore as tracers in distribution system research using the experimental systems at the Water Village, and 7) develop prediction models ANNs based on experimental data and modeling tools and 8) delineate a procedure for condensing CFD output on room air velocity and turbulence intensity fields into transition probabilities for the Markov

matrix. Translate the geometry of the CFD node system to the simpler geometry of the Markov chain model.

Project II: Infectious Disease Models for Assessing Microbial Risk and Developing Control Strategies

PIs: Joseph N.S. Eisenberg and James Koopman, University of Michigan

The primary accomplishments in Project II include 1) development of transmission models with explicit description of environmental contamination, 2) development of dynamic dose-response models to be integrated into transmission models, 3) evaluation of statistical models for analyzing efficacy of intervention trials, 4) collection of environmental contamination data during Influenza season to inform environmental transmission models.

By modeling transmission we aim to gain a better more complete understanding of the environmental risk process. We are addressing the effects of realistic settings by using stochastic rather than deterministic models, by modeling both transmission and the environment, and by modeling the dynamic aspects of the dose response relationship. Our work has already shown that explicitly incorporating the environment into the models results in slower disease spread dynamics in epidemics than those predicted by deterministic models without the environment. Taking into account an immune-based dose-response model shows us that probability of infection might depend not only on the dose but also in the time of exposure. As a result different routes of transmission have different associated risk levels. More realistic models lead to more realistic interventions. We found that the efficacy of intervention depends on the coverage as well as contact patterns between individuals.

In the Year-3, Project II will investigate 1) cumulative dose models with heterogeneous susceptibility to infection, 2) integration of cumulative dose-response into transmission models, 3) environmental sampling during the study of viral disease 4) role of environmental contamination in point source of norovirus outbreaks and subsequent secondary spread into households within the state of Michigan, and 5) induced bias from improper model assumptions: a simulation study.

Project III: Dose Response Assessment

PI: Charles N. Haas, Drexel University and Carole Bolin, Michigan State University

The primary accomplishments in the Project III include developing dose-response models for category A agents, i.e. *B. anthracis*, *Variola major* (smallpox), *Yersinia pestis*, Ebora, Marburg, Lassa, and *Francisella tularensis*. Dose-response for XDR (drug resistant TB) was also investigated. Development and approval of experimental dose studies for *F. tularensis* investigating oral exposures and cumulative dose.

The dose-response model most likely to apply to human inhalation anthrax is an exponential dose-response model with k = 1.65e-5. The LD50 for inhalation anthrax is estimated to be 41,930 organisms and the LD10 is estimated to be 6360 organisms. Based on differences in dose-response models fit to data for inbred and out-bred guinea pigs, inbred guinea pigs are significantly more sensitive to subcutaneous exposure to Lassa virus than their out-bred counterparts. Because data for response to aerosol exposure to Lassa virus were available only for out-bred guinea pigs, no conclusions can be drawn regarding the relative sensitivity of inbred and out-bred guinea pigs to aerosol exposure to Lassa virus or the influence on exposure route on susceptibility. This study demonstrates the need for experiments in which greater numbers of animals are exposed to Lassa virus and for experiments conducted with all the relevant exposure routes (subcutaneous, aerosol and ingestion). Developed approach to modeling incubation of *F. tularensis* in mouse organs. This result identified classes of dose response models which

predicted microbial growth and provided more appropriate sub-models for development of mechanistic dose response algorithms. These kinetic models are advancement on the traditional ones used for in-vivo growth and can aid in determining when to commence treatment of the disease and how aggressively to prosecute that campaign. The study provided the first quantification of the age effect on dose response models for *V. major*.
In the Year 3, Project III will progress through more developments of mechanistic dose response models based on microbial kinetics and human physiology. Microbial growth rate data will be used to develop realistic relations for in vivo growth and death. Output from the growth model will be used to predict the probability of infection associated with a given initial microbial dose. Using human physiology as a base for this mechanistic model advancement on the current dose response model will be proposed and analyzed this coming year. Established dose response models will be validated using available epidemiological data. The animal studies will inform the further development of these models.

Project IV: Assessment-Analysis Interface
PIs: Patrick Gurian[1], Elizabeth Casman[2], Mitchell Small[2], and Julie Downs[2], [1]Drexel University, [2]Carnegie Mellon University

The primary accomplishments Project IV include 1) evaluation of neighborhood-level disinfection as a strategy to provide drinking water after the contamination of a water distribution system 2) fit of a Bayesian hierarchical dose-response model, 3) development of a mass-balance compartment model to predict fomite surface concentrations and risk after a release of *B. anthracis*, 4) design of mental models, 5) creation of an influence diagram for influenza transmission, and 6) development of an interview protocol.
Understanding the relationship between environmental sampling and risk may help provide guidance to clean up efforts after a microbial contamination event. It is important to understand the extent of interspecies variability in dose-response models in order to interpret studies involving surrogate species. For example, it can inform the estimation of an appropriate interspecies safety factor in management decisions. The method developed for preparing risk communication content should help communicators deliver messages containing all the important concepts for dynamic and/or complicated risk situations. The plague dynamics model is an example of environmental reservoirs playing a significant role in on-going disease risks and thus can be used to address a complex agent, data needs and communication strategies. The Plague model can be used to evaluate the ability of plague to become established in urban rodent populations. Data that is routinely collected: flea index and rat carrying capacity, are used to locate the ecosystem in a phase diagram with regions of plague stability and plague burn-out.

In the Year-3, Project IV will 1) complete validation of compartment model and verify correspondence between environmental surface concentrations and human risk, 2) Complete validation of dose-response hierarchical model and explore an additional pathogen, probably tularemia, 3) explore a new framework in which the dose-response parameters for different species are modeled as deriving from correlated distributions, rather than from a single distribution, 4) extend *B. anthracis* scenario to include costs and benefits of alternative risk-based standards for microbial contamination, 5) carry out semi-structured interviews and web survey.

Project V: Knowledge Management, Transfer, and Learning
PIs: Rosina Weber, Michael Atwood, and Hyoi Han, Drexel University

The primary accomplishments in the Project V include update and of CAMRA Knowledge Repository (KR) version 1.7 by 1) revising learning units, 2) revising review process, 3) assessing

similarity (verbs, algorithm for taxonomy, testing trigram), and 4) building taxonomy. KR version 2.0 is currently under development based on these accomplishments.

The work from Project V members as knowledge facilitators is to support members of all other projects. The approximate number of approved units in Year 2 is 70. Around 350 units were reviewed in years I and II. CAMRA uses the Kellogg Foundation Logic Model as part of its evaluation process, which requires the capturing of the impact of the research, i.e. how it brings CAMRA closer to achieving its goals. The KR version 2 will add a new field "Impact" to document the impact of the research can demonstrate how the findings of that unit can help achieve the overall goals of CAMRA.

In the Year-3, Project V will complete and implementation of KR version 2.0. Specific tasks include 1) applying survey and conducting analysis, 2) conducting usability test, 3) revising and launching stable version, 4) applying survey and conducting analysis after version 2, and 5) reasoning with learning units for knowledge discovery

Integrated Projects:

In the Year-2, PIs have actively collaborated with other PIs beyond project group and universities. Some of integrated projects included tracer study at the Water Village, investigation of surrogates, examination of microbial recovery and attenuation on fomites, and investigation of influenza outbreak as well as a cryptosporidiosis outbreak. CAMRA developed a rapid alert associated with the risk of TB transmission by an infected individual during air travel. A risk estimate with a CAMRA Alert was facilitated by the CAMRA Co-Directors Rose and Haas together with Dr. Nicas, Dr. Masago, Ms Jones and Dr. Bartrand, a publication is currently in preparation.

Appendices

Publication

(Peer reviewed journals)

1. Boone, S. A. and C. P. Gerba 2007. The significance of fomites in the spread of respiratory and gastrointestinal disease. Applied and Environmental Microbiology, 73:1687-1696.
2. Weber, R. O. "Addressing Failure Factors in Knowledge Management," (2007). Electronic Journal of Knowledge Management, 5(3): pp. 333-346. Online: http://www.ejkm.com/volume-5/v5-i3/Weber.pdf
3. Weber, R. O. & Gunawardena, S. Designing Multifunctional Knowledge Management Systems. Accepted for publication in the proceedings of the Hawaii International Conference on System Sciences (HICSS-41), January 2008.
4. Weber, R. O., Gunawardena, S. & Proctor, J. M. Generating Reports from Case-Based Knowledge Artifacts. In D. Wilson & G. Sutcliffe (Eds.), Proceedings of the Twentieth International Florida Artificial Intelligence Research Society Conference (FLAIRS 2007) Menlo Park CA: AAAI Press.
5. Romero, P., C. K. Ho, and C. Y. Choi, 2007, Mixing at Cross Junctions in Water Distribution Systems – Part I. A Numerical Study, ASCE Journal of Water Resources Planning and Management (in press).
6. Austin, R. G., B. van Bloemen Waanders, S. McKenna and C. Y. Choi, 2007, Mixing at Cross Junctions in Water Distribution Systems – Part II. An Experimental Study, ASCE Journal of Water Resources Planning and Management (in press).
7. Pujol JM, Eisenberg JNS1, Haas CN; Koopman JS. 2007. The Effect of Ongoing Exposure Dynamics in Dose Response Relationships. Submitted to PNAS.
8. Sinclair, R., S. Boone, C. P. Gerba, D. Greenberg, D. Wagner and P. Keim. 2007. Persistence of select agents category A in the environment. Accepted Applied and Environmental Microbiology.
9. Verónica Corella-Barud, Kristina D. Mena, Shawn G. Gibbs, Patrick L. Gurian, and Alberto Barud. 2007. Evaluation of Neighborhood Treatment Systems for Potable Water Supply, submitted to International Journal of Environmental Health Research.
10. Haas et al. Dose-Response Models for Inhalation of Bacillus anthracis Spores: Interspecies Comparisons. Risk Analysis (Currently under Review)
11. Haas et al.Quantification of the Effects of Age on Dose Response of Variola major in Suckling Mice. Risk Analysis. (Currently under Review)
12. Haas et al.Dose Response Model for Lassa Virus. International Journal of Human Ecology & Risk Assessment (In Press)

(Un-refereed documents)

1. Shibata, T., Gurian, P, Rose JB., Haas, CN., Choi, C., Nicas, M., and Koopman, J., 2007. *Instruction manual for quantitative microbial risk assessment (QMRA)*. CAMRA 2nd QMRA Summer Institute, Michigan State University, East Lansing, MI.

Presentations
(Conferences)

1. Mitchell-Blackwood J., P. Gurian, M. Weir. Accepted for Dec. 2007 Society for Risk Analysis Meeting, "A Bayesian statistical modeling approach for *Bacillus anthracis* dose-response data".
2. Masago, Y. and Rose, JB. Risk-based analysis of cryptosporidiosis outbreak at recreational water spray park in New York State. International Water Association (IWA) Health Related Water Microbiology (HRWM) Symposium, Tokyo, Japan, September 9-15, 2007.
3. Shibata, T. and Rose JB. 2007. Quantitative microbial risk assessment of water-related disasters (Poster). International Water Association (IWA) Health Related Water Microbiology (HRWM) Symposium, Tokyo, Japan, September 9-15, 2007.
4. Sinclair, R. and Gerba, CP. 2007. Criteria for Microbial Surrogates for Assessing Fate and Transport of Pathogens in the Environment (Poster). International Water Association (IWA) Health Related Water Microbiology (HRWM) Symposium, Tokyo, Japan, September 9-15, 2007.
5. Koopman JS, Pujol JM, Eisenberg JNS. Infection Acquisition Dynamics and Timing of Exposure Doses. Society of Epidemiological Research (SER), Boston, Massachusetts, June 19-22, 2007.
6. Shibata, T. Advances in microbial risks toward enhancing water supply securityater security. American Water Works Association (AWWA) Michigan Water Security Summit, Lansing, MI, June 6, 2007.
7. Henley,JB., Boone,SA., Rose, JB., and Gerba, CP. Determining Inactivation Rates of MS-2 Coliphage on Fomites (Poster). 107th General Meeting of the American Society for Microbiology (ASM), Toronto, Canada, May 21-25, 2007.
8. Herzog, AB., Pandey, A., Shibata, T., Rose, JB., and Hashsham, SA. Implications of detection limit of various methods of Bacillus anthracis in computing risk to human health (Poster). 107th General Meeting of the American Society for Microbiology (ASM), Toronto, Canada, May 21-25, 2007.
9. Masago, Y and Rose JB. Risk assessment of the cryptosporidiosis outbreak at a recreational water spray park in New York State107th General Meeting of the American Society for Microbiology (ASM), Toronto, Canada, May 21-25, 2007.
10. Alok K. Pandey, Amanda B. Herzog, Joan B. Rose, Syed A. Hashsham. Potential of Quantum Dots as Surrogates for Microbial Pathogens and Evaluation of Their Genotoxicity. 107th General Meeting of the American Society for Microbiology, Toronto, Canada, May 21-25, 2007.
11. Shibata, T., Cologgi, DL, Masago, Y., Shumate, WJ., Williams, LB., Dials, K., and Rose, JB. Evaluation of virus recovery methods from fomites using a Virus surrogate, bacteriophage P22 (Poster). 107th General Meeting of the American Society for Microbiology (ASM), Toronto, Canada, May 21-25, 2007.
12. Jade Mitchell-Blackwood, J., P.L. Gurian, and M. Weir. "A Bacillus Anthracis Dose Response Model" Ninth Annual Research Day at Drexel University, Philadelphia, PA, April 17th, 2007.
13. Casman, E. and Fischhoff, B. Risk Communication Planning for Dynamic Situations: the aftermath of a plague bio bio-attack, DHS Summit on Research and Education), Washington, DC, March 15-6, 2007
14. Ho, C. K., Choi, C. Y., and S. McKenna, Evaluation of Complete and Incomplete Mixing Models in Water Distribution Pipe Network Simulations, World Environmental and Water Resources Congress, Tampa, FL, May, 2007.

15. Austin, R. G., Romero, P., and C. Y. Choi, Transport Phenomena at Intersections at Low Reynolds Numbers, World Environmental and Water Resources Congress, Tampa, FL, May, 2007.
16. Romero, P., Austin, R. G., and C. Y. Choi, Prediction of Contaminants in Water Distribution Systems using Artificial Neural Networks, World Environmental and Water Resources Congress, Tampa, FL, May, 2007.
17. Jade Mitchell-Blackwood, J., P.L. Gurian, and M. Weir. "A Bacillus Anthracis Dose Response Model" Ninth Annual Research Day at Drexel University, Philadelphia, PA, April 17th, 2007.
18. Choi, C. Y. Water Quality Modeling at the Water Village, Annual Department of Homeland Security University Network Summit on Research and Education, Washington D.C., March 15-16, 2007.
19. Mark H. Weir, Charles N. Haas, Timothy A. Bartrand. Effect of Host Species on the Dose-Response of Inhaled Bacillus anthracis Spores (poster). Annual Department of Homeland Security University Network Summit on Research and Education, Washington D.C., March 15-16, 2007
20. Bartrand, T.A., Kurugatta, B.B., Haas, C.N. Dose Response Modeling of Yersinia pestis (Plague Causitive Organism) Reveals High Levels of Dispersion. Annual Department of Homeland Security University Network Summit on Research and Education, Washington D.C., March 15-16, 2007
21. Casman, E. Public Communication Needs for Plague Bioterrorism Incidents. Society for Risk Analysis (SRA) Annual Meeting, Baltimore, Maryland December 3-6, 2006 .
22. Gurian, Dudley Ward, and Kenyon. Responding to anthrax contamination: Listening to surfaces and talking to people. Society for Risk Analysis (SRA) Annual Meeting, Baltimore, Maryland December 3-6, 2006.
23. Mark H. Weir, Charles N. Haas. Quantification of the Effect of Host Age on Dose-Response of Variola major in Suckling Mice. Society for Risk Analysis (SRA) Annual Meeting, Baltimore, Maryland December 3-6, 2006.
24. Mark H. Weir, Charles N. Haas, Timothy A. Bartrand. Effect of Host Species on the Dose-Response of Inhaled *Bacillus anthracis* Spores (poster). Drexel University Research Day. Drexel University,April, 2007
25. Mark H. Weir, Charles N. Haas, Timothy A. Bartrand. Effect of Host Species on the Dose-Response of Inhaled *Bacillus anthracis* Spores.; First Annual Drexel University Research Symposium , April, 2007
26. Bartrand, T.A., Kurugatta, B.B., Haas, C.N. Dose Response Modeling of *Yersinia pestis* (Plague Causitive Organism) Reveals High Levels of Dispersion (poster). Drexel University Research Day, April, 2007
27. William McGarry, Timothy A. Bartrand, Charles N. Haas. The Application of Food Microbial Growth Models to in-vivo *Francisella tularensis* Growth in Laboratory Animals. Drexel REU Student Poster Sessions, August, 2007
28. Rose, JB. Advancing Microbial Risk Assessment; AEESP Distinguished lecturer, Michigan Technology University, Nov. 9-10, 2006 AND AT:
29. Arizona State University, Nov. 13-15, 2006
30. Oklahoma University, Dec. 7-8, 2006
31. McGill University, Feb. 7-8, 2007
32. North Carolina State, March 26-27, 2007
33. University of Reno, April 5-6, 2007
34. Texas A&M, April 12-13, 2007

(**CAMRA workshops)**
1-day QMRA workshop, American Society for Microbiology (ASM) General Meeting, Toronto, Canada, May 20, 2007

- Rose, JB: Risk frameworks, data sets and integration of microbiological fields
- Haas, CN: Dose-response
- Shibata, T: Exposure assessment
- Gurian, P: Risk Characterization and management

2nd QMRA Summer Institute, Michigan State University, East Lansing, MI, August 19 -23, 2007.

- Rose, JB: Microbes and public health
- Rose, JB: Introduction to QMRA
- Gurian, P: Statistics and uncertainty
- Gurian, P: Maximum likelihood fitting
- Haas, CN: Animal experiment vs. epidemiological study
- Haas, CN: Dose-response models
- Haas, CN: Monte-Carlo simulation
- Rose, JB: Method for detection of microorganisms
- Shibata, T: Exposure Assessment
- Choi, C: Fate & transport: Water distribution system
- Nicas, M: Fate & transport: Air and fomites
- Koopman, J: Infection transmission models
- Gurian, P: Risk perception, communication, and management
- Gurian, P: Bootstrap uncertainty analysis

1-day QMRA workshop, International Water Association (IWA) Health Related Water Microbiology (HRWM) Symposium, Tokyo, Japan, September 9, 2007.

- Rose, JB: Risk frameworks, data sets and integration of microbiological fields
- Haas, CN: Dose-response
- Gerba, CP: Exposure assessment
- Masago, Y: Risk Characterization and management

Learning Units

Investigators	Status of Year-2 Tasks
Dr. Joan B. Rose Co-Directors MSU (Postdoctoral) Dr. Yoshifumi Masago Dr. Tomoyuki Shibata	(Completed) • 1-day QMRA workshop at ASM 2007 General Meeting: LU996 • 1-week QMRA Summer Institute 2007: 1038 • Evaluation of Swab and Wipe Methods for Viruses and Non-Spore Bacteria Recoveries from Nonporous Surfaces: LU1048 • QMRA Instruction Manual 1st edition: LU1050 (In progress) • Gathering data on Cryptosporidium outbreak at Seneca Park, NY in Aug 2005: LU 608 • Investigation of sampling methods for virus on fomites; PRD1 recovery and inactivation coefficient: LU609 • Investigating the risk of pathogen exposures to children from sewage-contaminated beach sand risk assessment, pathogens, sewage spill, beach sand: LU619 • Effectiveness of UV-HVAC system for improving indoor environmental quality in a hospital: LU1125
Dr. Charles P. Gerba Dr. Ian L. Pepper Univ. of Arizona Project I (Postdoctoral) Dr. Stephanie Boone Dr. Ryan Sinclair (Grad student) Jessica Henley Florence Fong	(Completed) • Investigating inactivation rates: LU 544 (In progress) • Axial dispersion of MS-2 phage in a model water distribution system :LU 1181
Dr. Chris Choi. Univ. of Arizona Project I (Postdoctoral) Dr. Inhong Song (Grad student) Ryan Austin Pedro Romero-Gomez	(Completed) • Dispersion of BAC in water distribution systems LU 456 • Complex Network Modeling Prediction using Water Quality Models and Artificial Neural Network LU 701 • Examination of the Perfect Mixing Assumption in Water Quality Models Dispersion patterns in water distribution systems LU 706 • Pattern Recognition and Axial Dispersion Artificial Neural Network LU 707 • Modeling and Experimental Verification of Water Distribution Systems LU 813 (In progress) • Completing mixing at intersections LU 1160 • Salt tracer transport study in a small scale 5 by 5 water pipe networks. LU 1131

	• Axial dispersion of MS-2 phage in a model water distribution system LU 1181 • Artificial Neural Networks for Modeling Water Quality in Pressurized Water Systems. LU 1153
Dr. Syed Hashsham MSU Project I (Postdoctoral) Dr. Alok Pandey (Grad student) Amanda Herzog	(Completed) • Environmental Detection Limit of Bacillus anthracis in Soil: LU 1166 • Environmental Detection Limit of Bacillus anthracis in Air: LU 1169 • Environmental Detection Limit of Bacillus anthracis in Water: LU 1171 • Instrument Detection Limit of Bacillus anthracis: LU 631 • Genotoxicity assessment of quantum dots using Comet assay: LU1202 (In progress) • The Evaluation of Detection Limit for qPCR and Plaque Assay Using Bacillus thuringiensis and P22 from Large Surface Areas: LU 1165 • Update for years 2006-2007 for the Detection Limit of All Methods for Bacillus anthracis: LU 1172 • Evaluating quantum dots (QDs) as surrogates: Activity is release, dispersion, and recovery of surrogates; Matrix is air, water, soil, or surfaces: LU 738 • Quantum Dots as surrogates for microorganisms: LU 1203
Dr. Joseph Eisenberg Dr. James Koopman Univ. of Michigan Project II (Postdoctoral) Dr. Josep M. Pujol (Grad students) Dr. Nottasorn Pilat Ian Spicknall Sheng Li	(Completed) • Developed dynamic dose-response models and fit to experimental data (LU 1025, 1026) • Developed environmental infection transmission system (EITS) model (LU 1117, 1122) • Examined the importance of contact patterns in efficacy of interventions (LU 1186) • Evaluated statistical models for analyzing efficacy of intervention trials (LU 1187) (In progress) • Collected environmental contamination data during influenza season (LU 1086)
Dr. Charles N. Haas Co-Directors, Drexel Project III (Postdoctoral) Dr. Tim Bartrand (Ph.D. Students)	(Completed) • Dose-Resonse model for Ebola virus and Marburg virus LU 1014, LU 1007 • Dose Response Model for Lassa Virus LU 983, LU 985 • Growth models for in vivo growth of Francisella tularensis LU 1102 • Quantifying age the effect of age on the dose-response of Variola major in suckling mice. LU1175 LU 1179 • Candidate Dose-Response Models for Subcutaneous and

Yin Huang Sushil Tamrakar Mark H. Weir	Inhalation Exposure to Yersinia pestis LU 1100 (In progress) • Fitting dose response models to Variola major data LU 719 • Q Fever dose response modeling LU 1142 • Dose-Response of Burkholderia pseudomallei (Melioidosis) LU 1006 • Development of mechanistic dose-response models LU 1105
Dr Carole Bolin MSU Project III	(In progress) • Dose-Response for oral exposure to Tularemia in a mouse model
Dr. Patrick Gurian Drexel Project IV (Grad student) Jade Mitchell-Blackwood	(Completed) • Evaluation of neighborhood level water treatment as a short-term response option LU 1063 (In progress) • Bayesian hierarchical dose-response modeling for anthrax: LU 498 • Analysis of existing data from neighborhood water treatment system: LU1089 •
Dr. Elizabeth Casman Dr. Mitchell Small Dr. Julie Downs Carnegie Mellon Project IV	(Completed) • Plague scenario development: LU 573 • Demonstration of an integrated assessment-inspired communications planning tool: LU574 (In progress) • Designing and conducting mental models study LU 576 • Flu transmission mental models project LU 868 • Creating influence diagram of influenza transmission LU 1010 • Developing interview protocol LU 1031
Dr. Rosina Weber Dr. Michael Atwood Drexel Project V (Grad student) Sidath Gunawardena Marcia Morelli	(Completed) • Revising research activity field in learning units LU 1209, LU 1210 • Adding Impact Field while Revising learning unit field structure LU 1207, LU 1208 • Revising learning unit field structure LU 1072, LU 1073 • Revising of Learning Unit Review Process for CAMRA KR Version 2.0 LU 1075, LU 1077 • Building a taxonomy LU 1082, LU 1083 • Assessing similarity between Research Activity Verbs LU 1084, LU 1085 • Comparing similarity metrics LU 1191, LU 1192 (In progress) • Designing CAMRA KR version 2.0 LU 1189 • Algorithm for traversing domain taxonomies LU 1193 • Implementing CAMRA KR Version 2.0 LU 1194

CAMRA Directors report Dr. Joan B Rose

Goals and Key Accomplishments:

CAMRA has two main goals:

- The first: Develop critically reviewed and interpreted sets of models, tools and information that will be used in a credible risk assessment framework to reduce or eliminate health impacts from deliberate use of biological agents of concern (BAC) as bioterrorists agents in the indoor and outdoor environment are available.

- The second: Build a national network for MRA for knowledge management, learning and transfer, for the community of scientists, community of students via educational programs and community of professionals in the field and in our communities has been established.

Goal 1

In this case efforts by Dr Rose have been undertaken to facilitate the PI's research projects and interactions. From an administrative standpoint the following were accomplished.

1. All year 2 statement of tasks were developed and all Sub-awards were established with the six other universities in a timely manner.
2. The QAPPs were received, reviewed and edited and finally accepted by Dr. Haas or Dr. Rose (Attachment Table A), working directly with Ms. Becca Ives.
3. Compliance forms and check lists were completed for DHS for every laboratory and University which is apart of CAMRA. (Available upon request)
4. The All PI meeting was organized at Carnegie Mellon University Feb. 28- March 1, 2007
5. Dr. Rose worked directly with Ms Jan Urban Loraine to address the Kellogg Logic Model for CAMRA. This will lead to an assessment tool for Year 3. (See Attachment B).
6. Dr. Rose made visits to PIs, and Govt scientists to address research progress and needs as follows:
    a. Univ. Of Arizona, Chuck Gerba, Chris Choi, Ian Pepper, Chuck Haas, Patrick Gurian, Liz Casman, Joe Eisenberg, Oct. 2006
    b. Univ. MI, Joe Eisenberg, Jim Koopman December 2006
    c. EPA Cincinnati January 3-4, 2007
    d. DHS meeting San Antonio, January 29-30, 2007
    e. Drexel; Patrick Gurian, Rosina Weber and Chuck Haas Feb. 1-2
    f. DHS, DC meeting for Centers March 14-16, presentations Joan Rose, Chuck Haas, Syed Hashsham, Rachael Jones.
    g. Met with Science Advisory Committee (SAC) member, Dr. Suresh Pillai, Texas A&M.
    h. UC Berkeley, April 24-25, 2007
    i. PNNL April 25-26, 2007
    j. CDC, Chuck Haas and Joan Rose, met with SAC member Dr. Stephen Morse, gave seminars and interacted with fomite and outbreak groups. July 10-12, 2007.
    k. Drexel, Patrick Gurian, Rosina Weber and Chuck Haas, Oct 31, 2007
7. Conference calls were set up and run
    a. Feb. 14th Carole Bolin (with Joan Rose, Tomoyuki Shibata, Paul Keim and Chuck Haas).
    b. April 30th All PI
    c. May 14th, All PI

d. July 9th, All PI
e. Nov. 2, All PI

8. Research Endeavors Facilitated by Dr. Rose included:
    a. Began a study with Univ. Michigan on the sampling of fomites for Influenza and Staphlococci. This was done in conjunction with Dr. Shibata
    b. Addressed the genetic characterization of P22 and developed a QPCR method for the phage. Used the phage in a fomite survival study with Dr. Shibata and Dr. Masago
    c. Set up a risk estimate response to the TB infected patient with a CAMRA Alert (with Dr. Haas, Dr. Nicas, Dr. Masago, Ms Jones and Dr. Bartrand). This is now being prepared as a manuscript.
    d. Began work on air and fomites in the hospital environment with the goal to evaluate UV HVAC systems for controlling bactera. With Dr. Shibata
    e. Began study of contact disinfectants for the control of bacteria, viruses, spores and toxins for a "safe tap" concept. Done in conjunction with the DHS summer fellow, Mr. Josh Mosberg
    f. Continued work on the application of Markoff Chain and risk modeling for the assessment of a Spray Park *Cryptosporidium* outbreak. With Dr. Masago (Dr. Nicas) and NY State Health Dept.
    g. Developed an assessment of the 10,000 mortality threshold based on numbers of people exposed, Probability of infection models and mortality rates. This is will be used to explore more realistic scenarios regarding intentional releases of BAC.

Goal 2

The effort within goal 2 was focused on CAMRA communications outside of the PIs, though the QMRA summer institute and other types of workshops and lectures.

1. Lectures on Microbial Risk Assessment were undertaken
    a. Michigan Technology University, Nov. 9-10, 2006
    b. Arizona State University, Nov. 13-15, 2006
    c. Oklahoma University, Dec. 7-8, 2006
    d. McGill University, Feb. 7-8, 2007
    e. North Carolina State, March 26-27, 2007
    f. University of Reno, April 5-6, 2007
    g. Texas A&M, April 12-13
2. QMRA Workshop was undertaken at American Society for Microbiology in Toronto, Canada, May, 2007. Reviews were excellent and ASM has requested that we run the workshop again in 2008. This was in conjunction with Dr. Shibata, Dr. Masago, Dr. Haas, and Dr. Gurian.
3. QMRA workshop was presented in Tokyo Japan at the IWA Health-Related Water Microbiology meeting. While EPA funds are not allowed to be used for international work, DHS is encouraging this acitivity, which was supported by the local organizers. This was in conjunction with Dr. Shibata, Dr. Masago, Dr. Haas, and Dr. Gerba.
4. The Summer Institute was run and funding was obtained from Battelle to support member attendance outside of CAMRA students. Five new CAMRA students attended. This was run in conjunction with CAMRA PIs and Dr. Shibata. A Science Advisory Committee (SAC) Member Dr. Rebecca Parkin attended and provided a report back to Dr. Rose.

TABLE A

Project	**QAPP #**	**PI**	**E-mail Address**	**University**	**Current QAPP Title & Version**	Date QAPP Submitted to QAO	Comments made by QAO* and returned to PI	Date QAPP Approved by QAO	Date QAPP Submitted to EPA	Comments made by EPA and returned to CAMRA	Date QAPP Approved by EPA
I	1	Chuck Gerba	gerba@Ag. arizona.edu	AZ	QAPP P1Q1 Gerba v2_0.doc	03/14/07	07/23/07	**07/31/07**	08/01/07	**08/31/07**	
I	2	Chris Choi	cchoi@arizona.edu	AZ	QAPP P1Q2 Choi v2_0.doc	03/27/07	04/11/07	**04/16/07**	04/26/07	**08/08/07**	**08/08/07**
I	3	Syed Hashsham	hashsham@ msu.edu	MSU	QAPP P1Q3 Hashsham v2_0.doc	03/27/07	04/11/07	**04/12/07**	04/17/07		
I	4	Mark Nicas	mnicas@berkeley.edu	UCBerkeley	QAPP P1Q4 Nicas v2_0.doc	4/9/2007	04/10/07	**04/12/07**	9/10/2007*	**08/08/07**	
I	5	Paul Keim (David Greenberg) (David Wagner - QA)	Dave.wagner@NAU.EDU	NAU	QAPP P1Q5 Keim v2_0.doc	03/27/07	04/11/07	**04/13/07**	04/17/07		
II	6	Jim Koopman - QA Joe Eisenberg (Joseph Pujol)	jkoopman@umich.edu	UM	QAPP P2Q6 Koopman v2_0.doc	04/04/07	04/09/07	**04/11/07**	04/12/07		
III	7	Chuck Haas	haas@ drexel.edu	Drexel	QAPP P3Q7 Haas v2_0.doc	03/28/07	04/04/07	**04/10/07**	04/12/07	**04/23/07**	
III	8	Carole Bolin	bolinc@msu.edu	MSU	QAPP P3Q8 Bolin v2_0.doc	04/09/07	04/11/07	**04/11/07**	04/12/07	**04/23/07**	
IV	9	Patrick Gurian	plg28@drexel.edu	Drexel	QAPP P4Q9 Gurian v2_0.doc	04/04/07	04/10/07	**04/17/07**	04/17/07		
IV	10	Liz Casman	casman@andrew.cmu.edu	CMU	QAPP P4Q10 Casman v2_0.doc	04/02/07	04/05/07	**04/13/07**	04/13/07		
V	11	Rosina Weber	rosina.weber@drexel.edu	Drexel	QAPP P5Q11 Weber v2_0.doc	04/08/07	04/10/07	**04/13/07**	04/13/07		

Attachment B

CAMRA ALL PI Meeting
February 27-March 1, 2007
Meeting Summary

Background

A second annual CAMRA All PI meeting was held on February 27- March 1, 2007 at Carnegie Mellon University, Pittsburgh, Pennsylvania. This report contains the following information pertaining to the meeting and meeting proceedings:

- Meeting agenda and list of participants (See Attachments 1 and 2)
- 2005-2006 project activity outputs
- Cross-project collaboration to occur during 2007
- Observations and recommendations for future project direction and management

The meeting proceedings included a number of updates and presentations: Logic Model Overview (Attachment 3); EPA Update; DHS Update; and CAMRA PI reports.

This summary was compiled by Jan Urban-Lurain, Spectra Data & Research.

Work to Date: Project Activity and Outputs from 2005-2006

The meeting agenda included an introduction to using a logic model approach to program implementation and results management.* Using this framework, project results from CAMRA Year 1 activities are summarized in Tables 1.0 and 2.0 below. Outputs have occurred in each project, with the greatest number of project-specific outputs generated from the activities of Project I. Three publications based on project activities and outputs have been completed to date. The Center sponsored one Institute (2006); in addition, Center scientists and students have participated in three other workshops and presented at eight other conferences/meetings.

* *Adapted from W.K. Kellogg Foundation Logic Model Development Guide, January 2004*

Table 1.0 2005-2006 CAMRA Project Results Summary

Table 1.0 summarizes the project activity *outputs* achieved during 2005-2006 along with the longer range intended *outcomes and impacts*.

Projects	Project Goals/Outputs (2005-2006)	Outcomes	Impact
Project I – Exposure, Detection, Fate and Transport of Agents	▪ Identified practical anthrax surrogate (*Bacillus thuringiensis)* ▪ Identified most sensitive anthrax detection method (real time polymerase chain reaction) ▪ Identified virus survival rates ▪ Determined need to improve existing code related to mixing at intersections of water distribution systems ▪ Completed update of Markov chain particle model	▪ New experimental protocol for the assessment of BAC fate and transportation in aerosols and water ▪ An accurate modeling of water quality ▪ Prediction tools to better simulate solute transport ▪ Enhanced capacity to predict airborne concentrations and deposition of microbial agents of concern	▪ Greater knowledge and capacity to address risk associated with intentional or accidental contamination events
Project II – Infectious Disease Models for Assessing Microbial Risk and Developing Control Strategies	▪ Created pathogen characteristic database ▪ Developed models for: 1)single object – contamination; 2) single venues that incorporate multiple objects; 3) multiple venues	▪ An alternative taxonomic classification of infectious pathogens ▪ Inform the development of decontamination control strategies	
Project III – Dose Response Assessment	Developed fitting dose response models for 1)inhaled *Bacillus anthracis* and 2) yersinia pestis	▪ Improved dose response information for assessing human risk of exposure from inhaling B. anthracis spores; smallpox; and	

		hemorrhagic viruses	
Project IV – Assessment-Analysis Interface	New method for risk communications planning for complex scenarios	▪ Reduction in key decision uncertainties related to urban aerosol plague attacks ▪ Response plan guidance for regulators ▪ Priorities for research to reduce key uncertainties	
Project V – Knowledge Management, Transfer, and Learning	Initiated operation of the knowledge repository version 1.0	▪ Close critical MRA framework data gaps; provide information to reduce uncertainties	

Table 2.0 2005-2006 Workshops, Publications, and Presentations

Table 2.0 represents presentation and publication *outputs across all projects.*

Workshops (Across all projects)	▪ QMRA Summer Institute (2006) ▪ Infectious Disease Informatics ▪ National Academy of Sciences ▪ National Conference on Environmental Sampling and Detection for Bio-Threat Agents
Publications (Across all projects)	▪ The significance of fomites in the spread of respiratory and gastrointenstinal disease, *Applied and Environmental Microbiology* ▪ No time to think: Preparing for Post-Bioattack Communications *(In review)*
Presentations (Across all projects)	▪ Public Communication Needs for Plague Bioterrorism Incidents (*Social Risk Analysis Annual Meeting*) ▪ Transport Phenomena at Intersections of Pressurized Pipe Systems (*8th Annual Water Distribution Systems Analysis Symposium*) ▪ Risk Assessment for Biosecurity (*Doctoral Program Day, University of Michigan*) ▪ Assessing Infection Risks and Control Options when Transmission is Person-to-Person via Multiple Routes Across Diverse Venues (*Society for Risk Analysis*) ▪ DHS Centers for Excellence Meeting ▪ Responding to anthrax contamination: Listening to

	surfaces and talking to people (*Society for Risk Analysis)*
Publications and Presentations	▪ Identifying the Core of an Emerging Multidisciplinary Domain (*Proceedings of the 69th Annual Meeting of the American Society for Information Science and Technology*) ▪ Designing a Knowledge Management Approach for CAMRA Community of Science

Moving Forward: 2007 and Beyond

1. Feedback from Breakout Sessions

All project teams participated in team-to-team breakout sessions during the meeting. Questions used during the breakout discussions included:

- What outcome(s) are shared across these projects? How do the activities/outputs from each project intersect?
- What are implications of these intersections on resources and activities?
- What additional and/or different resources are needed? How do we need to modify activities to ensure success in reaching outcomes?

Table 3.0 Team-Identified Cross-Project Collaborations

Table 3.0 lists areas for cross-cutting activities identified during breakout session discussions. Much of the identified cross-project activity focuses on the transmission of Project I outputs to Project II and the institution of dialogues between Project II and Projects III and IV.

	Project I	**Project II**	**Project III**	**Project IV**	**Project V**
Project I				Interdisciplinary education component for training associated with risk assessment	
Project II	Project II wants generalizable fate and transport information ▪ Project I aerosol release experiment outputs will be an (input →) for Project II ▪ Surrogates and exposure from Project		▪ A model inclusive of time to outcome to available data ▪ Begin explicit dialogue with Project III about flu data	Begin explicit dialogue with Project IV	

	I will be (inputs →) to Project II ▪ Need more about model scenarios to to explore implications of experimental design				
Project III		Begin explicit dialogue with Project II about flu data		Shared interests around dose response for anthrax	
Project IV		Need Project II large area surface wipe results to link to Project IV			
Project V	Incorporate impacts into learning units	Incorporate impacts into learning units	Incorporate impacts into learning units	Incorporate impacts into learning units	Incorporate impacts into learning units

2. Observations from the Scientific Advisory Committee (SAC)

The meeting offered SAC members a first opportunity to engage with the project teams. SAC members' observations corroborate a need for *strengthened cross-project collaboration* as CAMRA moves forward.

The committee's observations are summarized below.

Table 4.0 SAC Observations – CAMRA ALL PI Meeting, February 27-March 1, 2007

Background	CAMRA is an ambitious program and the investigators need to be commended for conceptualizing the project in its scope and marshaling the resources. This project is highly relevant to a broad range of societal needs.
Strengths	▪ Strong scientific talent with broad and specific expertise ▪ Multi-disciplinary teams ▪ Support of the USEPA and DHS ▪ All the steps – and more – needed for risk assessment is covered.

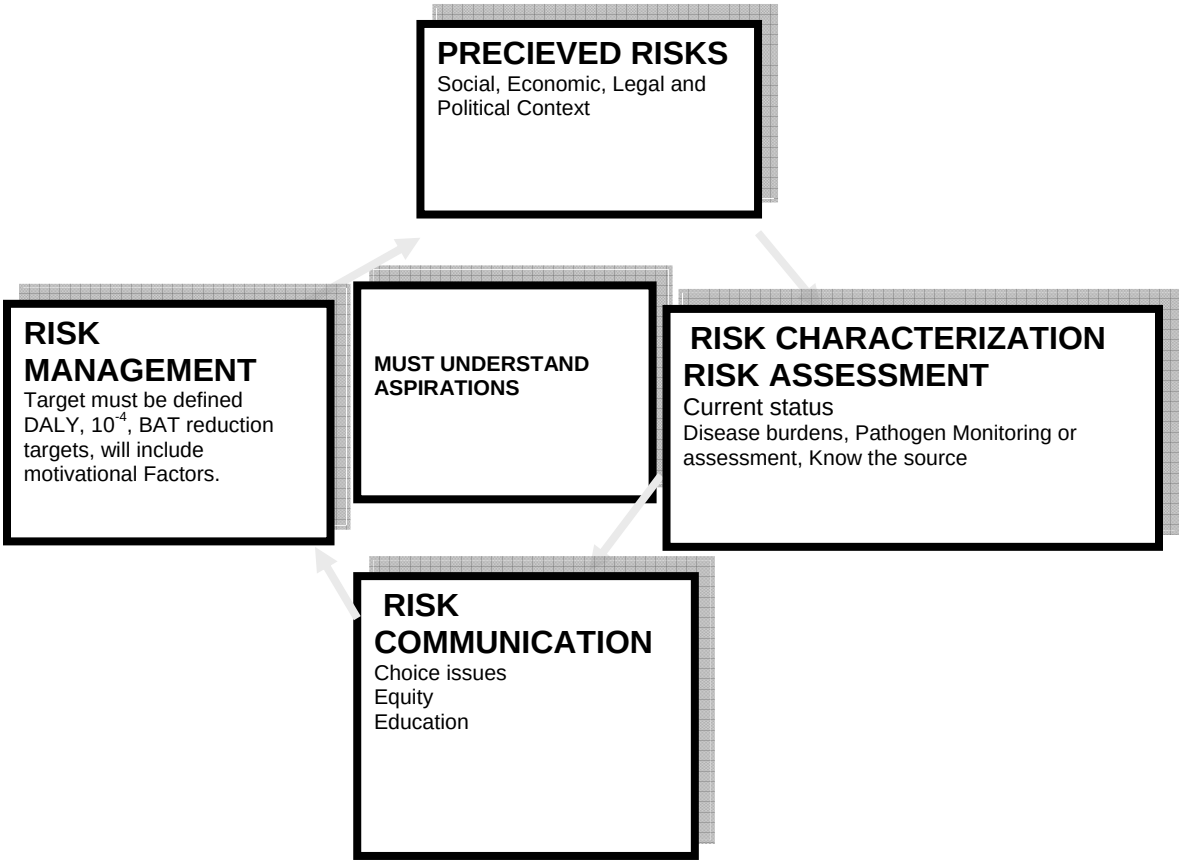
	▪ Appropriate financial resources appear to be available ▪ Research is on the cutting-edge of national priorities
Perceived Challenges	▪ Projects depend on each other intellectually and temporally much more than the investigators may realize. The true and overall value of the project depends on strong coordination, which may not be fully in place. ▪ Translation and risk communication are important elements to achieve major impacts. ▪ One limitation is a lack of a "docking space" for definitions, assumptions and scientific protocols (e.g., assuring consensus on the quality, type and time scale of data are crucial for ensuring the interdisciplinary applications of the project). These are key elements that if not adequately tracked early on could have significant negative impacts on the Center's productivity. ▪ Students appear to have limited opportunities to interact across campuses. ▪ There appears to be a disconnect in terms of the organisms being studied amongst the different projects. This may imply that key characteristics of pathogens need to be considered to ensure that the choices of experimental designs and surrogates are optimal. ▪ Systematic attention to quantifying uncertainty appears to be lacking. ▪ The justification of surrogates for select agents appears to be based on data availability and logistics rather than correlation with true infectious disease threats. ▪ A unifying scientific framework for the Center's research portfolio is not readily apparent.

3. Considerations for CAMRA's Future

Co-Director Dr. Joan Rose outlined a proposed direction and future vision for the CAMRA. Key elements in her proposal are:

- The first: critically reviewed and interpreted sets of models, tools and information that will be used in a credible risk assessment framework to reduce or eliminate health impacts from deliberate use of biological agents of concern (BAC) as bioterrorists agents in the indoor and outdoor environment are available.

- The second: a national network for MRA for knowledge management, learning and transfer, for the community of scientists, community of students via educational programs and community of professionals in the field and in our communities has been established.



Recommendations

1. *SAC Recommendations*. SAC recommendations emphasize building inter-project links; defining unified, clear scientific goals; and translating the science to have a strong impact. Specifically, there is need for:

    A. A mechanism for a stronger integration and coordination of the project goals.
    B. A clearer definition of key scientific unifying goals.
    C. A mechanism for the translation of the science and the communication of the outcomes to make a strong impact.
    D. Greater mentoring and interactions among student colleagues across campuses.
    E. The quantification of uncertainty should be central to experimental design, and should be considered in the Center's research priorities. Extensive use of surrogates for modeling transmission and exposure of select agents may introduce unquantifiable uncertainty.

2. *Other Programmatic Recommendations.*

    A. Refine and clearly articulate overall CAMRA program outcomes. The use of the Logic Model to assess program implementation status identified a need for better articulation of outcomes for *each* project's activities as well as for *overall* Center activity. Doing this planning will further pinpoint where collaboration is needed across the projects (Recommendation 1.A) as well as provide a focus for tracking the Center's progress.

    B. Develop a clear CAMRA statement of impact. The proposed direction and future articulated by Dr. Rose are a starting point for continued discussion of the intended long term implications and value of the CAMRA work. Having dialogue and reaching

closure on intended impact is key to addressing recommendation 1.C above

C. Establish program evaluation questions and indicators. Thinking through these questions and related indicators is a means to articulating expected successes and a groundwork for sharing with others the successes and lessons learned from the program. Having clear success indicators and supporting data are also key to addressing recommendation 1.C.

Attachment 1 – Meeting Agenda

Agenda **Tuesday February 27th**

4:00-5:00PM SAC INTRODUCTIONS and CAMRA UPDATES

5:00-5:30 LOGIC MODEL OVERVIEW

Agenda **Wednesday February 28th**

8:30-9:00AM WELCOME and WHOLE GROUP INTRODUCTIONS

9:00- 9:45 EPA UPDATES

9:45-10:30 DHS UPDATES

10:30-11:00 BREAK

11:00-12:30 CAMRA PI REPORTS

12:30-1:45 LUNCH

1:45 – 2:00 BREAK

2:00- 5:00PM LOGIC MODEL WORKSHOP PART I: FOCUS on RESULTS

2:00 - 2:45 CAMRA IMPACTS/VISION
2:45 - 3:00 CHARGE TO THE PROJECT BREAKOUT GROUPS
3:00 - 4:25 PROJECT OUTPUTS and OUTCOMES – BREAKOUT Groups

4:25 - 4:50 END OF DAY DEBRIEF

Agenda **Thursday March 1**

8:45 - 9:00 CHECK IN AND CHARGE FOR THE DAY

9:00- 2:15 LOGIC MODEL WORKSHOP PART 2: CONNECTING ACROSS PROJECTS

9:00 - 10:15 CROSS-PROJECT BREAKOUT GROUPS

10:15 - 10:30 BREAK

10:30 - 11:45 CROSS-PROJECT BREAKOUT GROUPS

11:45 – 1:00 LUNCH

1:00 -2:15 CROSS PROJECT BREAKOUT GROUPS

2:15 – 2:30 BREAK

2:30 – 3:15 LOGIC MODEL WORKSHOP PART 3: PROJECT REVIEW and REVISIONS

3:15 – 4:00 PROJECT GROUP REPORT OUT

4:00 - 4:15 MEETING WRAP-UP and ADJOURNMENT

Attachment 2 – List of Participants

No	Name	School	Email Address
1	Joan Rose	MSU	rosejo@msu.edu
2	Amanda Herzog	MSU	herzoga2@msu.edu
3	Tomoyuki Shibata	MSU	tshibata@msu.edu
4	Carole Bolin	MSU	bolinc@dcpah.msu.edu
5	Todd Ewen	MSU	toddewen@cvm.msu.edu
6	Yoshifumi Masago	MSU	ymasago@msu.edu
7	Rebecca Ives	MSU	ivesrebe@msu.edu
8	Alok Pandy	MSU	alokkp06@msu.edu
9	Syed Hashsham	MSU	hashsham@msu.edu
10	Rebecca Parkin	SAC / George Washington University	parkinr@gwa.edu
11	Elizabeth Casman	Carnegie Mellon University	casman@andrew.cmu.edu
12	Mark Nicas	UC Berkeley	mnicas@berkeley.edu
13	Rachel Jones	UC Berkeley	rmjones@berkeley.edu
14	David Greenberg	Northern Arizona University	dlg2@nau.edu
15	Thomas Burke	SAC / John Hopkins	tburke@jhsph.edu
16	Suresh Pillai	SAC / Texas A&M University	spillai@poultry.tamu.edu
17	Gertjan Medema	SAC / University of Arizona	gertjan.medema@kiwa.nl
18	Ryan Austin	University of Arizona	rgaustin@email.arizona.edu
19	Pedro Romero	University of Arizona	pedromer@email.arizona.edu
20	Ryan Sinclair	University of Arizona	ryan.gaice@gmail.com
21	Christopher Choi	University of Arizona	cchoi@arizona.edu
22	Chuck Gerba	University of Arizona	gerba@ag.arizona.edu
23	Joseph Eisenberg	University of Michigan	jnse@umich.edu
24	Joseph M. Pujol Serra	University of Michigan	jmpujol@umich.edu
25	James S. Koopman	University of Michigan	jkoopman@umich.edu
26	Ian Spicknall	University of Michigan	ispickna@umich.edu
27	Sheng Li	University of Michigan	shengli@umich.edu
28	Nottasorn Plipat	University of Michigan	nplipat@umich.edu
29	Sushil Tamrakar	Drexel University	sbt26@drexel.edu
30	Mark Weir	Drexel University	mw88@drexel.edu
31	Jade Blackwood	Drexel University	jade@drexel.edu

32	Timothy Bartrand	Drexel University	tab32@drexel.edu
33	Charles Haas	Drexel University	haas@drexel.edu
34	Patrick Gurian	Drexel University	pgurian@drexel.edu
35	Rosina Weber	Drexel University	RW37@drexel.edu
36	Sid Gunawardena	Drexel University	sg349@drexel.edu
37	Kelvin Soldat	Pacific Northwest National Library	kelvin.soldat@PNL.gov
38	Cindy Sonich-Mullin	EPA	sonich-mullin.cynthia@epa.gov
39	Andy Avel	EPA	avelandy@epa.gov
40	Deborah McKean	EPA	mckean.deborah@epa.gov
41	Angela Page	EPA	Page.Angelad@epa.gov
42	Holly Ferguson	EPA	ferguson.holly@epa.gov
43	Irv Baumel	EPA	baumel.irwin@epa.gov
44	John Hall	EPA	hall.john@epa.gov
45	Gene Rice	EPA	rice.gene@epa.gov
46	Rob Rothman	EPA	rothman.rob@epa.gov
47	Tonya Nichols	EPA	nichols.tonya@epa.gov
48	Jon Kaye	EPA	kaye.jonathan@epa.gov
49	Chandrika Moudgal	EPA	moudgal.chandrika@epa.gov
50	Femi Adeshina	EPA	adeshina.femi@epa.gov
51	Kenneth Tucker	Battelle	tuckerkd@Battelle.org
52	Phil Koga	DTRA	philip.koga@dtra.mil
53	Jan Urban-Lurain	Spectra	janul@aol.com

CAMRA OUTLINE FOR ANNUAL REPORTS

Project: Exposure: Detection, Fate and Transport of Agents

Investigator: Charles P. Gerba and Ian L. Pepper

Project Goals (from proposal, additional goals):

Tasks for Year (II):

The primary task goals of year two were to conduct an extensive literature review to identify data gaps on the survival of agents of concern on fomites and potential surrogates, the development of criteria for selection of surrogates, and develop a protocol for assessing decay constants for agents of concern and surrogates on fomites.

Research Activities:

A literature review as completed on the decay rates of select agent category A in water, air and on fomites. This information was then used to calculate normalized inactivation rate constants for the different agents. This information was placed into tables and an article prepared that assessed the current state of knowledge and needs for future research. We determined that little of the existing information was in a form that could be used to develop inactivation rate constants except in the broadest terms. It was concluded that more detailed experiments are need where environmental conditions are better defined and that enough time points are sampled during the decay process are collected as to provide more precision in the data if it is be used in modeling.

Several methods were studied to define the best methods of sampling for surrogates and select agents on different types of fomites. Three different methods were tested for the recovery of viruses from fomites. These were nylon swab, Fellowes wipes and vortexing the test material in Trypticase soy broth. Coliphages MS-2, coliphage P-22 and poliovirus type 1 (strain LSc-2ab). All methods give similar recovery rates from the fomites. The lowest recovery of the viruses was from cloth materials, however. The viruses survived the longest on cloth materials. Initial die-off constant for these viruses are now being developed along with Picinde virus which is being used as a surrogate for arenaviruses (e.g. Lassa fever virus).

A document was prepared on criteria that should be used when selecting surrogates for select agents. The document also provides of list of potential surrogates for select category A agents and the rationale for potential application. This document will be provided to other CAMRA investigators and other individuals for review and comment before submission for publication.

Background and prior research:

While the study of microbial persistence on fomites has been conducted by numerous investigators no attempt to normalize the data from different studies has been. In addition, identification of all the significant factors influencing the decay has not been summarized until this study. While various surrogates have been used for agents of concern, the selection of criteria has not yet been defined, especially in reference to objectives.

Research Contributions this Year:

LU 544

To be useful in model predictive models on the fate of agents of concern information on their decay on fomites needs to be normalized from various studies published in the literature. The existing literature on the survival of enteric and respiratory viruses was reviewed and data on virus decay was normalized against environmental conditions reported by the various students review. This data is now available for use in models to predict survival of these agents on fomites. It was found that enteric viruses survive for days to months on surfaces compared to hours to days for respiratory viruses.

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Outputs:

8.1 Students Supported and/or Graduated:

Stephanie Boone (postdoctoral fellow – research associate), now working with the Agriculture Research Service, USDA

Jessica Henley (M.S. student, in progress)

Florence Fong (M.S. student, in progress)

8.2 Publications:

Boone, S. A. and C. P. Gerba 2007. The significance of fomites in the spread of respiratory and gastrointestinal disease. Applied and Environmental Microbiology, 73:1687-1696.

Sinclair, R., S. Boone, C. P. Gerba, D. Greenberg, D. Wagner and P. Keim. 2007. Persistence of select agents category A in the environment. Submitted for publication.

8.3 Patents

None

8.4 Presentations:

"Criteria for Microbial Surrogates for Assessing Fate and Transport of Pathogens in the Environment" C.P. Gerba R. Sinclair and J. Henley. Presented at the 14th International Symposium on Health Related Water Microbiology. Tokyo, Japan. September 9-14, 2007

"Persistence of Coliphage MS-2 on Fomites" J. Henley and C. P. Gerba. Presented at the Annual Meeting of the American Society for Microbiology. Toronto, Canada. May, 2007.

8.5 Participation or organization of workshops:

Workshop on Quantitative Microbial Risk Assessment. Instructor. Tokyo, Japan, September 9, 2007

8.6 Case studies, algorithms developed: None

8.7 Human Resource Development: None

8.8 Other (consulting, interviews, etc.): None

8.9 Funds Leveraged (additional funding, resources for free):

Dr. Ryan Sinclair who works jointly with Dr. Choi received a Postdoctoral Fellowship from the Department of Homeland Security.

Ms. Florence Fong (M.S. graduate student) has a research assistantship from the University of Arizona

Outcomes:

The publication of normalized decay rates for viruses on fomites allows for the prediction of the survival agents of concern on common indoor objects (fomites). This can be used in models to assess the risk of infection to first responders or other exposed individuals after the release of an agent of concern in buildings.

Collaboration with other Projects (actual work in collaboration within and outside CAMRA):

Ryan Sinclair is working with Dr. Choi and his students on development of viral and other tracer tests for the distribution system network.

We have been working with Dr. Paul Keim and his graduate student about the parameters for developing data on the persistence and detection of *Bacillus antrhuis* and selected of appropriate surrogates for this pathogen. We have met several times with Dr. Keim and his graduate student David Greenberg to develop comparative data on decay models of agents of concern and surrogates in various environments.

I have met several times with Dr. Joan Rose and Dr. Chuck Haas to work on the methods and conditions to be used for the detection and assessment of decay rates on fomites for agents of concern and surrogates.

WE are working with personal in Dr. Rose's and David Greenberg standardized fomites for testing and testing methods for fomites.

Tasks for Next Year:

Assess the use of coliphages *E. coli* and a bacillus spore as tracer in distribution system research using the experimental systems at the Water Village (in collaboration with Dr. Choi), starting with the pipe intersection problem.

Complete laboratory research of on the decay rates of surrogates and agents of concern on fomites under a variety of conditions for use in predictive models. This will be done in

conjunction with Dr. Keim's group. Our group is tasked next year with developing decay rates of Picinde virus, yellow fever virus and two other viruses to be selected on fomites and in drinking water.

CAMRA OUTLINE FOR ANNUAL REPORTS

Project: Exposure: Detection, Fate and Transport of Agents
Investigator: Christopher Y. Choi
Project Goals (from proposal, additional goals): Modeling BAC in water systems (model development and design; field studies utilizing the Water Village)
Tasks for Year (II):
The primary task is to carry out experiments and develop accurate water quality modeling tools. The experimental systems are designed based on EPANET and revised water quality modeling tools. Computational Fluid Dynamics (CFD) is used to examine the accuracy of the EPANET. Using a 5x5 network, Artificial Neural Network (ANN) models are tested to identify the unknown parameters that lead to concentration histories, release locations, and the release time of hypothesized biological agents.
Research Activities:
LU 1160 (in progress) - Completing mixing at intersections
LU 1131 (in progress) - Salt tracer transport study in a small scale 5 by 5 water pipe networks.
LU 1181 (in progress) - Axial dispersion of MS-2 phage in a model water distribution system
LU 1153 (in progress) - Artificial Neural Networks for Modeling Water Quality in Pressurized Water Systems.

LU 456 (Completed) - Dispersion of BAC in water distribution systems
LU 701 (Completed) - Complex Network Modeling Prediction using Water Quality Models and Artificial Neural Network
LU 706 (Completed) - Examination of the Perfect Mixing Assumption in Water Quality Models Dispersion patterns in water distribution systems
LU 707 (Completed) - Pattern Recognition and Axial Dispersion Artificial Neural Network
LU 813 (Completed) - Modeling and Experimental Verification of Water Distribution Systems

Background and prior research:

Water quality models in water distribution systems have been examined. The movement of chemicals or biological agents is investigated via computational fluid dynamics simulations, water quality models, and experimental approaches. A series of computational simulations using selected geometries are carried out at various Reynolds numbers covering from laminar, transitional, to turbulent regimes. Boundary conditions, turbulence intensities, convergence criteria, and mesh sizes are thoroughly evaluated. The parametric study focused on pipe intersections to characterize complex mixing phenomena in pressurized water distribution pipe networks. Experimental verifications have been carried out at the Water Village, where the research infrastructure was completed during the first year.

Research Contributions this Year

Based on our recent work (Yr. 1, described in LU 706), the water quality model has been modified using the C programming language, and a provisional EPANET water quality code has been developed. We viewed that accurate mathematical descriptions of the behavior of nodal mixing under various network conditions are the keys to fulfilling the research objectives of microbial risk assessment. Our studies for nodal mixing in a cross junction have demonstrated that the incomplete nodal mixing is governed by the ratio of inflows, ratio of outflows, and concentrations of inflows, which can be described by dimensionless parameters such as the ratio of the Reynolds number and dimensionless concentrations (C^*). These facts were proven by

computational fluid mechanics (CFD) and experimental results (via flow visualization) as shown in Figure 1. Based on 'instantaneous' and 'complete' mixing assumption for the current EPANET, the concentration in all outflow pipes is expressed as:

$$C_{OUT} = \frac{\sum_{IN} C_i Q_i + S_j}{\sum_{OUT} Q_i} \tag{4}$$

where S_j denotes the source term. The equation simply describes the flow-rate-weighted average of the incoming and outgoing concentrations. Based on this 'incomplete' mixing assumption, on the other hand, the above equation should be rewritten as:

$$\sum_{OUT} C_i Q_i = \sum_{IN} C_i Q_i + S_j \tag{5}$$

Outgoing concentrations can be calculated using both Equations (1) and (5), where C_E* can be obtained from the recent experimental data for the modified EPANET.

A 5 by 5 water distribution network was designed on this code for multiple purposes such as validating mixing at junctions, building scenarios for microbial risk assessment, and predicting dispersion patterns using ANNs. Three sets of preliminary experiments with a 5 by 5 pipe network were conducted at the Water Village of the University of Arizona (LU 1131, in progress). The salt concentration values are recorded at total eight points, which include three drainage points (D) and five conductivity sensors (C), shown in Figure 2a. Each experimental set consists of locations of the conductivity sensors and draining points. The experiments were repeated three times, and the predicted concentration results are presented in comparison with measured values. The result of the data based on the incomplete mixing assumption was also hand-calculated to ensure the accuracy of the revised code. Figure 2b demonstrates the validity of the revised water quality model based on the incomplete mixing assumption. In this grid network, the Reynolds number ranges from laminar to transient to turbulent regimes (1,200 < Re < 36,500). In a network, it is almost impossible to avoid low Re zones, although the input Re at the bottom left corner in the Figure 2a is fully turbulent (Re = 36,500).

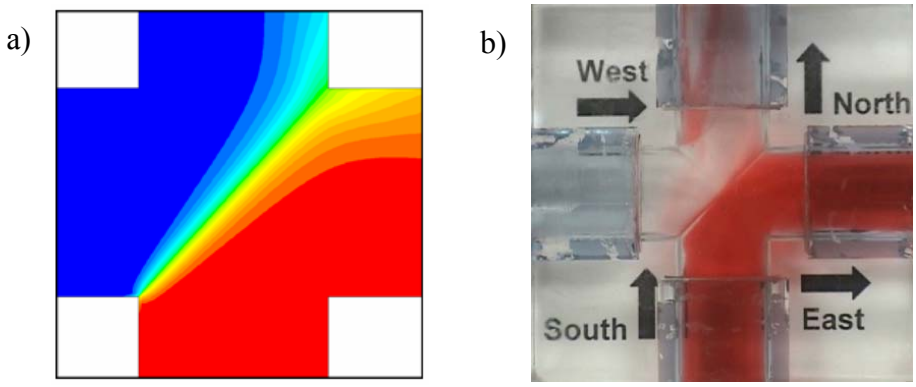

Figure 1. Flow Visualization at low Re using (a) CFD and (b) Experiment

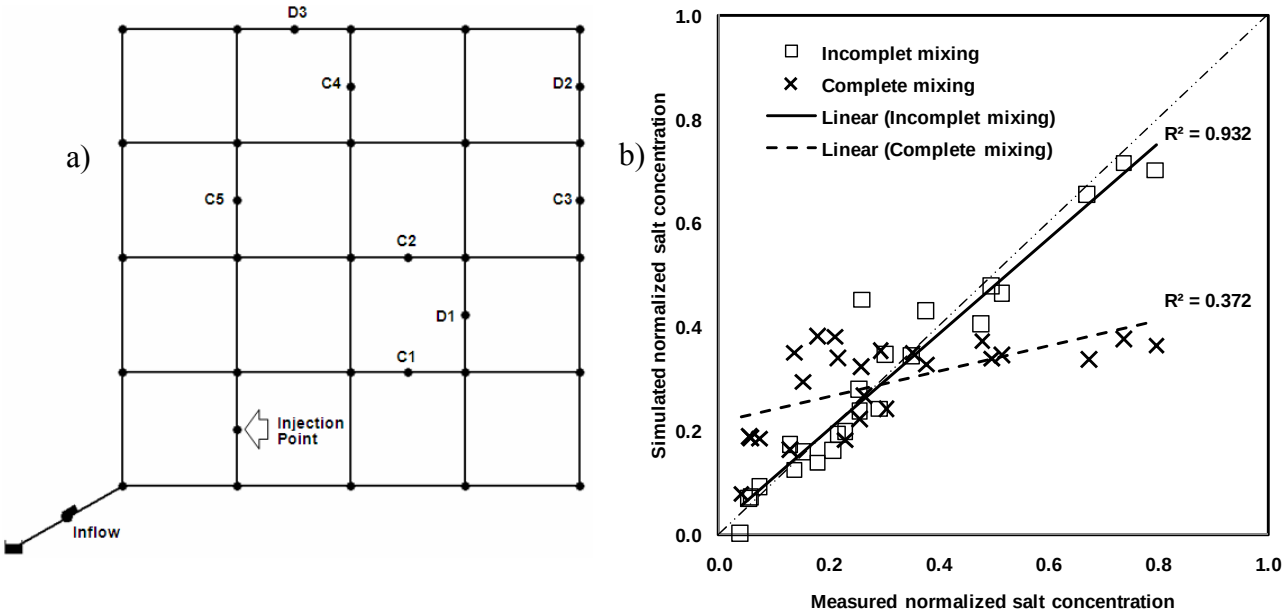

Figure 2. (a) A schematic of a 5x5 network for a preliminary experiential run. 'C' and 'D' denote conductivity sensor and drainage locations, respectively, and (b) preliminary test results in comparison with modeling results with complete and incomplete mixing assumptions.

An ANN trained on outputs from the modified EPANET model (based on non-perfect mixing, NPM, assumption at cross flows) produces more accurate results than an ANN trained on outputs from the original EPANET, where perfect mixing (PM) at junctions is assumed (LU 701). In order to test this hypothesis, the 5x5 water network shown in Figure 2a was used. It contained three random demand points (on mid-points and/or corners) and one fixed intrusion point.

A thousand EPANET files were created with MATLAB. Each of them contained a new set of demand points with different flow rates (Q_1, Q_2, Q_3) and locations (x_1, y_1, x_2, y_2, x_3, y_3) in a random manner. Two feed-forward ANNs with back-propagation learning algorithm were trained with MATLAB Neural Networks Toolbox 5.1. Each ANN had 20 units in the hidden layer, and was trained on different datasets. The outcome was an ANN trained on original assumptions (PM-ANN) and another ANN trained on modified assumptions (NPM-ANN). Outcomes from PN-ANN and NPM-ANN were compared to experimental results. An increase in R^2 for NPM-ANN indicates that outputs from modified EPANET are in general more reliable than those from original EPANET for the 5x5 network. The results also suggest that improvements on overall modeling accuracy are required, which may be achieved by one or more of the following modifications: (i) increase number of patterns up to 2000 or more, (ii) use modified ANN architecture and algorithm features, and (iii) add additional fixed locations within the network for concentration data, and thus and increase number of ANN outputs. LU 1153 (in progress) will further address these modifications.

We have also investigated the validity of the plug flow assumption using experimental and computational tools as described in LU 707. Nonlinear velocity profiles in laminar and

transitional flows can longitudinally spread the constituent, and therefore, the plug-flow assumption may result in incorrect concentration curves, as shown in Figure 3a. Convective transport phenomena are supposedly dominant, and thus the plug-flow assumption should hold in the turbulent flow regime. However, as presented in Figure 3b, turbulent velocity profiles may also become important, and the corresponding axial dispersion cannot be ignored.

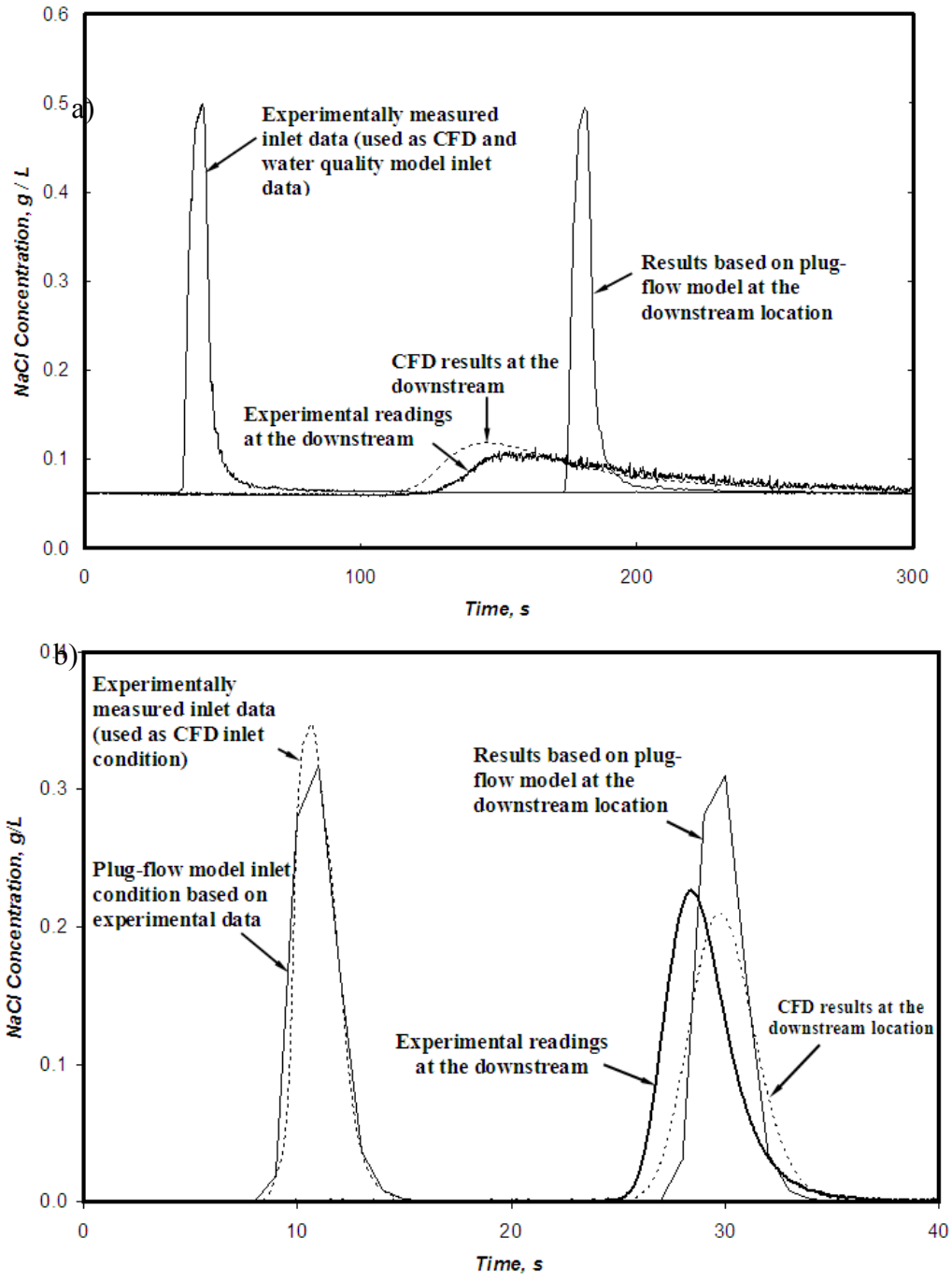

Figure 3. Axial dispersion in a straight pipe - preliminary results. (a) Re = 900; (b) Re = 6,600.

Next, the dispersion of microbes along a straight pipe with varying flow conditions was investigated. The experiments were successful in demonstrating that dispersion of MS-2 phage in

a straight pipe disperses similarly to a salt tracer and computational fluid dynamic (CFD) models. The overall shape of the dispersion for the three progressively faster flow conditions show a gradual pulse profile moving towards the shape of typical plug flow condition. For example, the concentration profile at Re = 5500 shows a consistent CFD and salt tracer breakthrough with the microbial data. The EPANET model lags behind as shown in Figure 4. Additional studies are currently underway (LU 1181, in progress).

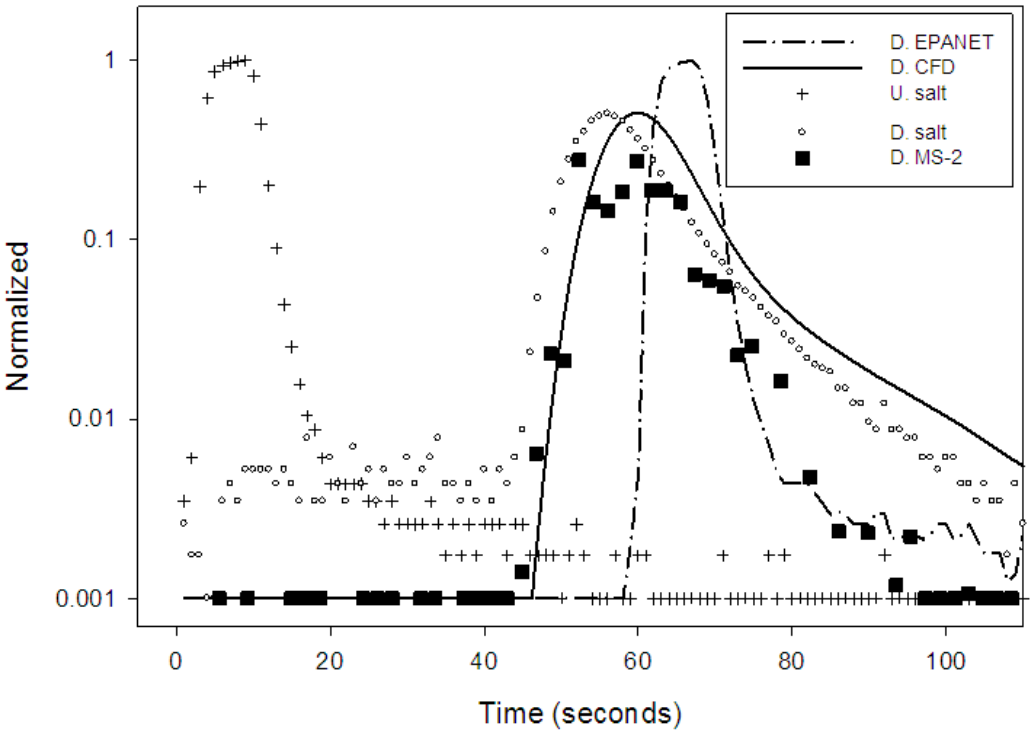

Figure 4. Dispersion of MS2 and Salt tracer at Reynolds number of 5500

Outputs:

8.1 Students Supported and/or Graduated:

Ryan Austin (M.S. Student, in progress)
Pedro Romero-Gomez (Ph.D. Student, in progress)

8.2 Publications:

Romero, P., C. K. Ho, and C. Y. Choi, 2007, Mixing at Cross Junctions in Water Distribution Systems – Part I. A Numerical Study, *ASCE Journal of Water Resources Planning and Management* (in press).

Austin, R. G., B. van Bloemen Waanders, S. McKenna and C. Y. Choi, 2007, Mixing at Cross Junctions in Water Distribution Systems – Part II. An Experimental Study, *ASCE Journal of Water Resources Planning and Management* (in press).

8.3 Patents: None

8.4 Presentations:

Ho, C. K., Choi, C. Y., and S. McKenna, Evaluation of Complete and Incomplete Mixing Models in Water Distribution Pipe Network Simulations, World Environmental and Water Resources Congress, Tampa, FL, May, 2007.

Austin, R. G., Romero, P., and C. Y. Choi, Transport Phenomena at Intersections at Low Reynolds Numbers, World Environmental and Water Resources Congress, Tampa, FL, May, 2007.

Romero, P., Austin, R. G., and C. Y. Choi, Prediction of Contaminants in Water Distribution Systems using Artificial Neural Networks, World Environmental and Water Resources Congress, Tampa, FL, May, 2007.

Choi, C. Y. Water Quality Modeling at the Water Village, Annual Department of Homeland Security University Network Summit on Research and Education, Washington D.C., March, 2007.

8.5 Participation or organization of workshops:

Lecture - Water Quality Modeling and Risk Assessment at the Quantitative Microbial Risk Assessment Summer Institute, Michigan State University, Lansing, MI, Sponsored by US EPA and DHS, August, 2007.

8.6 Case studies, algorithms developed:

Provisional algorithm and C code are developed for mixing at cross junctions

8.7 Human Resource Development: None

8.9 Other (consulting, interviews, etc.): None

8.10 Funds Leveraged (additional funding, resources for free):

Laboratory expansion funding from the Environmental Research Laboratory (Ian Pepper, Director).

NSF Grant No. EEC-0600855

NSF-sponsored Undergraduate Research Fellowship for a minority undergraduate student (Jolomi Iyoha)

Outcomes:

Our study will impact a wide variety of network analyses including prediction of disinfectant residuals, optimal locations for water quality sensors, prediction models for early warning systems, numerical schemes for inverse source identification, and quantitative risk assessment.

Collaboration with other Projects (actual work in collaboration within and outside CAMRA):

Collaboration with Chuck Gerba (Project I) – Preparation and injection of viruses and bacteria into the water distribution system.

Collaboration with Paul Keim (Project I) - Preparation and injection of spores into the water distribution system.

Integration with other projects (association between units in different projects):

Collaboration with Patrick Gurian (Project IV) – Develop intrusion scenarios and assess the quantitative risk assessment model.

Tasks for Next Year (see definition below):

Continue to fill in the database for mixing at junctions (particularly low Reynolds numbers) – LU 1160

Continue to investigate the accuracy of water quality models to predict dispersion patterns in water distribution networks – LU 1131

Develop prediction models using ANNs based on experimental data and modeling tools – LU1153

Inject surrogates into water distribution systems at the Water Village and examine the prediction models – LU 1181

Anticipated Technical Results and Developments:

Potential LU 1 - Mixing patterns at cross junctions for laminar, transitional, and turbulent flows

Potential LU 2 - Accuracy of water quality models to predict dispersion patterns of microbial agents in water distribution networks

Potential LU 3 - Prediction models based on ANNs using experimental data and modeling tools

Potential LU 4 – A Case Study; Dispersion of Biological Agents and Corresponding Risk Assessment

CAMRA OUTLINE FOR ANNUAL REPORTS

Project: Group 1; Exposure: Detection, Fate and Transport of Agents

Investigators: Dr. Paul Keim and Dr. David M. Wagner

Project Goals (from proposal, additional goals):

selection of potential surrogates for *Bacillus anthracis*

collection of laboratory data for selection of potential surrogates

provide parameters for fate and transport models

Tasks for Year (II):

The primary tasks of year two were to:

conduct an extensive literature review to identify the best potential surrogates for *Bacillus anthracis* to be used in fate and transport experiments

develop a protocol for preparing spores for use in fate and transport experiments.

conduct experiments to show the similarity between the characteristics of the spores

determine real world parameters for fate and transport models using experiments in air, soil, and on fomites

Research Activities:

investigating potential surrogates for *Bacillus anthracis*, identifying data gaps in our knowledge, and generating a review document

developing a reliable and reproducible spore purification method

generating comparative data on the persistence (*i.e.* fate and transport) of BACs and surrogates using various mediums (fomites, buffer, water, soil, etc.)

Background and prior research:

extensive and comprehensive literature reviews were employed to identify potential *B. anthracis* surrogates and potential spore purification methods. All references are compiled into an endnote library

Research Contributions this Year:

LU: (in progress – will be submitted soon)

A literature review was completed to select the potential surrogates for experimental validation as the best surrogate for *B. anthracis*. All information was collected and compiled into a review document outlining the history of use of surrogates for *B. anthracis*, and the experimental and physical evidence that would help us to decide which surrogate would theoretically be the best surrogate for *B. anthracis*, including genetic, morphological, and behavioral information.

LU: 1111

Several methods were examined to identify the best methods for preparing spores for use in our fate and transport experiments. Several methods from the literature were examined and tested. We focused on identifying a method that is fast, simple, cheap, reliable, and consistent.

Outputs:

Students Supported and/or Graduated:

a) David Greenberg (PhD in progress)

2) Publications:

a) Sinclair, R., S. Boone, C. P. Gerba, D. Greenberg, D. Wagner and P. Keim. 2007. Persistence of select agents category A in the environment. Submitted for publication.

b) Greenberg, D.L., D.M. Wagner, and P. Keim. 2007. Surrogate selection: A case study for *B. anthracis*. In preparation

3) Patents: None

4) Presentations: None

5) Participation or organization of workshops: None

6) Case studies, algorithms developed: None

7) Human Resource Development: None

8) Other (consulting, interviews, etc.): None

9) Funds Leveraged (additional funding, resources for free): None

Outcomes:

The spore purification method provides a standard procedure that is fairly consistent and easy to perform. The methods were deigned to be used within the CAMRA group, however, as the method is similar to methods already developed, others can use the protocol as well.

Collaboration with other Projects (actual work in collaboration within and outside CAMRA):

We have been working with Dr. Chuck Gerba, Dr. Chris Choi, and Ryan Sinclair to help develop a surrogate for *B. anthracis* to be used in fate and transport experiments. Several meetings have taken place to discuss surrogate use in these experiments and to train personnel in preparing spores for experiments.

We have also consulted with Jessica Henley in Dr. Gerba's lab to help prepare fomite experiments for persistence studies of *B. anthracis* and potential surrogates on steel, laminar, and plastic.

Tasks for Next Year:

1) Continue experimental comparison of several possible *B. anthracis* surrogates to be compared with *B. anthracis* Ames (a virulent strain) with the purpose of validating a surrogate for use in fate and transport experiments.
2) Continue experiments that will provide parameters for fate and transport models (*i.e.* decay rates for *B. anthracis* spores on several mediums (*i.e.* fomites, water, buffer, soil etc.).

CAMRA YEAR 2 REPORT
September 1,2006 through August 30,2007

Note: The official start date of the subaward for UC-Berkeley was September 1,2005, but grant funds were not available at UC-Berkeley until April 20,2006. The result is that while Year 2 officially covered the period September 1,2006 to August 31,2007, in practice it is covering the period April 20,2007 to April 19,2008.

1. Project: Development of a Discrete-Time Markov Chain Model for the Within-Room Transport and Fate of Airborne Microbial Agents of Concern

2. Investigators: Mark Nicas, PhD, CIH (PI) and William W. Nazaroff, PhD

3. Project Goals: There are three 5-year project goals, although only the first goal was to be addressed in Year 2. The three project goals are: (i) to develop and validate a Markov chain model to predict airborne particle-associated microbial transport and fate in indoor environments; (ii) to measure the resuspension into air of particle-associated microbes due to human activity; and (iii) to determine the particle size distribution of respiratory aerosol.

4. Tasks for Year 2 (September 1,2006 through August 31,2007):

Task 1 – Refine a simple Markov chain model to include particle transport by gravitational settling and particle loss by deposition onto the floor and other room surfaces.

Task 2 – Develop a method for translating velocity vector and turbulent intensity values, as generated by computational fluid dynamics modeling or direct measurement, into transition probabilities for the Markov chain particle model.

Task 3 – Initially validate the Markov chain particle model via comparing its predictions against appropriate published data.

Task 4 – Construct a test chamber or, in the alternative, arrange for the use of a test chamber or room in which to conduct aerosol release experiments for model validation.

Task 5 – Conduct aerosol release experiments. Component subtasks are (i) finalizing the decision on the inert particle sizes, nature of the particles, and analytical methods; (ii) finalizing the decision on the aerosol generation procedures; (iii) acquiring the equipment for generating the aerosols; (iv) acquiring the equipment for sampling air and surfaces for the test particles; (v)

acquiring expertise in generating the aerosols; and (vi) conducting replicate trials of the aerosol release experiments. Given the approximate 8-month delay in receiving the subaward funding, it was anticipated that the aerosol release experiments will extend into Year 3 of the grant.

Task 6 – Analyze the experimental aerosol release data. Data on particle concentrations in air and deposition onto the floor and walls at different room positions will be compared with predictions made by the Markov chain particle given, alternatively, (i) judgmental estimates of room air velocities and turbulence versus, (ii) measured values for room air velocities and turbulence, and (iii) if available, CFD estimates of room air velocities and turbulence.

Task 7 – Draft a manuscript reporting the data and the performance of the Markov chain model.

5. Research Activities:

Refining a simple Markov chain model (Task 1) – The Markov chain model for transport and fate of gas-phase contaminants was extended to particles. Gravitational settling was modeled by a first-order rate dependent on particle aerodynamic diameter, and deposition was modeled based on published algorithms for deposition velocity. The model accounts for particle transport via advective flow, turbulent diffusion and gravitational settling, and particle loss from room air by deposition onto the floor and other room surfaces (e.g., walls, ceiling) and by the room exhaust airflow. A particle-size dependent function for the rate of deposition onto walls and the ceiling was derived from measurement data.

Developing a method for incorporating information on air velocity and turbulent intensity values (Task 2) – The following algebraic approach was delineated. A three-dimensional air velocity vector can be posed at each room position at each moment in time. This vector can be measured with directional anenometry equipment, or by computational fluid dynamics (CFD) modeling. The distribution of three-dimensional vectors over time at the room position forms a type of "wind rose". The average of this distribution is the average velocity vector; in turn, the average vector is decomposed into average components along the orthogonal x, y and z axes. The magnitude (speed) of each average component (e.g., $\overline{\mathbf{X}}$) is used to assign a rate of particle movement due to advective flow along the corresponding axis. The difference between each instantaneous component vector and its average vector (e.g., $\mathbf{X} - \overline{\mathbf{X}}$) is defined as a residual vector **Xres**. The distribution of the magnitude (speed) of the residual, denoted $|\mathbf{Xres}|$, has mean $\mu_{|\mathbf{Xres}|}$ and variance $\sigma^2_{|\mathbf{Xres}|}$. Similar distributions of residual speeds pertain along the y and z axes. A turbulent intensity metric denoted *k* is the square root of the sum of the variances of the three residual speed distributions. If the three distributions of residual speeds are independently and identically distributed (or treated as such for simplicity), the turbulent diffusion coefficient D_T in the Markov chain model is a linear function of the turbulent intensity metric *k*. In summary, D_T is an idealized parameter that permits symmetry in the dispersion of a particle along three orthogonal axes in the Markov chain model, and under special conditions it is a function of the turbulent intensity metric used to quantify variability in air speeds along these same axes.

We also plan to investigate an empirical approach for relating turbulent intensity and D_T via the time-to-mixing concept. Given a pulse release of a tracer gas agent at a single room position, the time to mixing τ_{mix} is defined as the time it takes for the percent coefficient of variation of the tracer concentration at different room positions to decrease to 10%. In a sealed room, the percent coefficient of variation will eventually decrease to zero, because the tracer gas will disperse uniformly throughout the room. In a given test room, we can determine τ_{mix} by releasing CO gas and subsequently measuring the CO concentration at multiple room positions via real-time CO monitoring instruments. We have available for our use multiple real-time CO meters with data-logging capability. We can also map room air velocities and fluctuations via three-dimensional anenometry, such that we can relate turbulent intensity to τ_{mix}. In addition, via the Markov chain model for the given room dimensions, we can find a D_T value that corresponds to τ_{mix}. Thus, via their relationships with τ_{mix}, we seek to establish an empirical relationship between turbulent intensity and D_T.

Initially validating the Markov chain model using published data (Task 3) – We considered published experimental data for the floor deposition of cobalt oxide particles released in a building lobby (E Sajo, et al., "Spatial distribution of indoor aerosol deposition under accidental release conditions," *Health Physics 83*:871-883, 2002). Sajo and colleagues conducted four replicate tests of the release, and sampled deposition at approximately fifty floor positions. The cobalt oxide particle size distribution, and average air velocities at numerous room positions, were reported. The Markov chain particle model predicted a pattern of floor deposition similar to the observed pattern, with maximum floor deposition occurring near the release position. The predicted mass deposition at approximately 50% of the floor positions was within the 95% confidence interval for the average mass observed to deposit at these same locations across replicate runs of the release experiment. We submitted a manuscript (titled "A Markov Chain Model for Supermicron Particle Transport and Fate in Indoor Air") describing this analysis, and our work under Tasks 1, 2 and 3, to the Journal of Occupational and Environmental Health. We received reviewer comments which have caused us to perform further analyses. We have not yet submitted a revised manuscript and a response to those reviewer comments with which we disagree.

Acquiring a test chamber for particle release experiments (Task 4) – We are confident that we will acquire a test room at the UC-Berkeley Richmond Field Station, which is located several miles (about 15 minutes by private vehicle) from the main campus. We are meeting with Dr. Scott Shackleton, Assistant Dean, Facilities and Management, College of Engineering, who controls space at the Field Station, and he has already indicated that he can accommodate our needs. Earlier in the year, Dr. Nicas toured space in an off-campus building owned by UC-Berkeley. However, subsequent to that visit, the UC-Berkeley sold the building. Although UC-Berkeley is renting the same building for the next three years, administrators decided not to permit new use of unoccupied space in the building. In addition, Dr. Nazaroff determined that a test chamber at the Lawrence Berkeley National Laboratory could be used for our project, but we would have to share the test chamber with other investigators and fit our experiments into their schedules. We judged this arrangement was not practical. In May 2006, Dr. Nicas and Rachael Jones (UC-Berkeley PhD student) had toured available space at the Water Village facilities at the University of Arizona. We decided that working at the University of Arizona involved too many logistical difficulties and travel expenses, and that the experiments needed to be conducted in Berkeley.

Conduct aerosol release experiments (Task 5) – We have not yet conducted aerosol release experiments due to the delay in securing a test space. However, we decided to use inert fluorescein-labeled particles generated from an isopropyl alcohol solution via a variable orifice aerosol generator (VOAG) owned by Dr. Nazaroff, with analyses conducted by flourometry. The goal is to generate particle sizes of 3 μm, 7 μm, and 15 μm. We have purchased and borrowed most of the equipment necessary for the experiments. We purchased two three-dimensional anenometers and a flourescein standard for the fluorometer. Using other funding, we purchased ten air sampling pumps, a meter for measuring carbon monoxide (CO), and CO gas. The CO will be used as a tracer agent to measure the air exchange rate in the test room. We have arranged for dedicated use of a flourometer owned by a faulty member in the College of Civil and Environmental Engineering, and an aerosol particle sizer owned by a faculty member in the Environmental Health Sciences Division, School of Public Health. Other sampling equipment (for example, filters and glass plates) will be purchased in the near future.

Analyze the experimental aerosol release data (Task 6) – Given that the aerosol release experiments have not been conducted yet, there has been no data analysis. Dr. Charles Haas, Drexel University, has indicated that a post-doctoral fellow in his research group would be able to model air flows in the test room via CFD techniques.

Draft a manuscript reporting the data and the performance of the Markov chain model (Task 7) – Given the present lack of experimental data, this task has not been started.

6. Background and prior research: A Markov chain model was developed to describe the transport and fate of gas-phase contaminants in indoor air. The model accommodates transport by advective airflow (bulk flow in an average direction) and turbulent diffusion (random air motion superimposed on the directional advective flow), and removal via exhaust airflow from the room. This work was presented in: Nicas M, **"**Modeling turbulent diffusion and advection of indoor air contaminants by Markov chains," American Industrial Hygiene Association Journal, Volume 62, pp 149-158 (2001). An application of the general Markov chain technique was modeling the airborne dispersion of small-diameter respirable particles carrying ***M. tuberculosis*** bacilli emitted by a patient with pulmonary tuberculosis, and estimating the consequent infection risk to room occupants. Because small-diameter particles have low gravitational settling rates, they were approximated as gas-phase contaminants. This work was presented in: Nicas M, "Markov modeling of contaminant concentrations in indoor air," American Industrial Hygiene Association Journal, Volume 61, pp 484-491 (2000). The current project extends the technique to supermicron particles which have substantial gravitational settling rates. The refined model includes the added transport mechanism of gravitational settling, and the added removal mechanism of deposition onto the floor and other room surfaces. In addition, the current project incorporates spatial information on air velocity and turbulent intensity to better assign the directional probabilities of particle movement.

7. Research Contributions in Year 2: The research conducted in Year 1 is described in Item 5, "Research Activities".

Task 1 is essentially 100% completed.

Task 2 is 50% completed. Remaining issues involve condensing the CFD output at thousands of room positions into transition probabilities for fewer cells in the Markov matrix, and translating the geometry of the CFD node system to the simpler geometry of the Markov chain model.

Task 3 is 100% completed.

Task 4 is 90% completed. Again, we are in the process of acquiring test sapce at the UC-Berkeley Richmond Field Station.

Task 5 is 50% completed in terms of deciding on the experimental protocol and acquiring equipment. Assuming the test room is obtained by the end of November, we would to begin experimental work in December 2007.

Task 6 is 0% completed.

Task 7 is 0% completed.

8. Outputs:

8.1 Students Supported and/or Graduated: The grant supported Rachael Jones, a PhD student, during the entirety of Year 2.

8.2 Publications: None at this time. However, we submitted a manuscript titled "A Markov Chain Model for Supermicron Particle Transport and Fate in Indoor Air" to the Journal of Occupational and Environmental Health.

8.3 Patents: None

8.4 Presentations: [Rachael]

8.5 Participation or organization of workshops: Dr. Nicas participated as an instructor in the CAMRA Summer Institute on Quantitative Microbial Risk Assessment, in August 2007.

8.6 Case studies, algorithms developed: The work conducted for Task 1 involved refining the Markov chain model, which can be considered an algorithm. The work conducted for Task 3 was a type of case study, because we considered the experimental data published by E Sajo, et al. (2002): "Spatial distribution of indoor aerosol deposition under accidental release conditions," *Health Physics 83*:871-883.

8.7 Human Resource Development: None

8.8 Knowledge Transfer: None yet beyond the CAMRA Knowledge Repository

8.9 Other (consulting, interviews, etc.): None

8.10 Funds Leveraged (additional funding, resources for free): We purchased air sampling pumps and a carbon monoxide meter with money provided by a training grant from the National Institute for Occupational Safety and Health. This funding was spent appropriately because the same equipment can be used by industrial hygiene students in their research projects. However, no industrial hygiene student has identified a project in which this equipment would be used in the next several months, so there are no scheduling conflicts. In addition, a non-CAMRA funded UC-Berkeley MS student who is interested in indoor air quality issues will participate in the research. This student will investigate the relationship between turbulent intensity (as measured via three-dimensional anenometry), time to mixing (as measured using CO tracer gas), and the Markov chain model's turbulent diffusion coeffcient parameter.

9. Outcomes:

Once reasonably validated, the Markov chain particle model would have diverse applications. It would facilitate predicting airborne concentrations and deposition of microbial agents of concern in indoor environments following intentional or accidental releases. It would also have broader public health applications, for example, predicting airborne concentrations and deposition of nonviable but toxic particulate contaminants due to releases in occupational and residential indoor environments.

10. Collaboration with other Projects:

We plan to collaborate with Dr. Charles Haas, Drexel University. A member of his research group would predict the air velocity and turbulent intensity fields in our test room via CFD modeling, and we would use that ouput to assign single-step transition probabilities in the Markov chain model. Via our three-dimensional anenometry measurements, we will assess the accuracy of the CFD predictions. Via our particle release experiments, we will assess the accuracy of any CFD predictions of particle deposition in the test room. At a future time, we hope to conduct analogous aerosol release experiments in collaboration with Dr. Charles Gerba, University of Arizona, using a biological agent such as a bacteriophage. The information on aerosol deposition that comes from these experiments will be used in Dr. Choi's and Dr. Gerba's project on the transport and fate of microbial agents of concern on fomites and room surfaces. However, we are not involved in Dr. Choi's and Dr. Gerba's separate project on the transport and fate of microbial agents of concern in water distribution systems.

11. Integration with other projects:

Please see Item 10, "Collaboration with Other Projects".

12. Tasks for Year 3:

Task 1 – essentially completed

Task 2 – Delineate a procedure for condensing CFD output on room air velocity and turbulence intensity fields into transition probabilities for the Markov matrix. Translate the geometry of the CFD node system to the simpler geometry of the Markov chain model.

Task 3 – completed

Task 4 – acquire the test space

Task 5 – Conduct the aerosol release experiments using inert fluorescein-labeled particles. Component subtasks are (i) acquiring expertise in generating the aerosols, and (ii) conducting replicate trials of the aerosol release experiments. It is anticipated that the aerosol release experiments will begin in December 2007 (officially in Year 3) and will take several months.

Task 6 – Analyze the experimental aerosol release data. Data on particle concentrations in air and deposition onto the floor at different room positions will be compared with predictions made by the Markov chain model given, alternatively, (i) judgmental estimates of room air velocities and turbulence versus, (ii) measured values for room air velocities and turbulent intensity, and (iii) if available, CFD estimates of room air velocities and turbulence.

Task 7 – If sufficient aerosol release experiments are conducted, draft a manuscript reporting the data and the performance of the Markov chain model.

Task 8 – Design the particle resuspension experiments as outlined in original Objective 6 of Project I.

13. Anticipated Technical Results and Developments:

Please see Item 9, "Outcomes".

1. Project: **Validation of detection methods: (Part of Project I. Exposure: Detection, Fate and Transport of Agents)**

2. Investigators: Syed Hashsham

3. Project Goals (from proposal, additional goals):

Document the frequency distribution of instrument and environmental detection limit for various methods used to detect biological agents of concern (BAC). Evaluate the detection limit of qPCR and plaque assay using *Bacillus thuringiensis* and P22 recovered from large surface areas. Evaluate the suitability of quantum dots as a surrogate for BAC.

4. Tasks* for Year (2):

(i) Document the distribution of detection limit and other parameters that influence the algorithm for quantifying risk for all BACs.

Evaluation of detection limits for plaque assay and qPCR with agents recovered from large surface areas.

Review the instrument and environmental detection limit for *Bacillus anthracis.*

(ii) Evaluate the performance of selected quantum dots as surrogates.

(iii) Genotoxicity assessment of quantum dots.

5. Research Activities (First field in learning units, starts w/ verb in -ing form, e.g., investigating):

Investigating instrument detection limits and environmental detection limits for *Bacillus anthracis.*

Evaluating detection limits from qPCR and plaque assay using P22 and *Bacillus thuringiensis* recovered from large surfaces.

Investigating quantum dots as surrogates.

Investigating genotoxicity of Quantum dots.

6. Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

Frequency distribution of detection limit of various methods for Bacillus anthracis: There is considerable amount of literature published on *Bacillus anthracis*. We were able to locate more than 1300 journal articles using a number of keywords with default years set from 1900-2006. These references are available in an EndNote file upon request. All abstracts were manually screened for significant articles on the detection of *Bacillus anthracis*. Approximately 100 references that were closely related to method development or validation were chosen for further analysis. Articles were first categorized either by instrument or environmental detection limit and then by method. Methods included for instrument detection limit are real-time PCR, PCR, microarray/PCR, biosensor, immunoassay, electrochemiluminiscence, Raman Spectroscopy, and mass spectrometry. Detection limits were extracted from the articles and normalized to the same units.

Instrument Detection Limit: The articles applicable to the detection limit of *Bacillus anthracis* in all available methods were sorted based on instrument or environmental detection limits. The

article where a method detects *Bacillus anthracis* from a pure culture and does not spike into a matrix (air, water, soil, and fomite) is considered to be the instrument detection limit. All detection limits from the instrument detection limit articles were extracted directly from the article; no calculation was needed to obtain the detection limit. Extracted raw data was recorded in units of cells, spores, DNA, colony forming units (CFU), protective antigen, and genomic copies in volumes that ranged from liters to micro liters. Articles that used units of protective antigens were not used in this literature review due to the unknown conversion to cells. All data was converted into standard units of cells per milliliter of reaction solution and graphs were made according to method.

Computation of Environmental Detection Limit: The studies that detected *Bacillus anthra*cis in a spike assay were considered to compute the environmental detection limit. Those studies were then categorized according to the matrix in which *Bacillus anthracis* was detected (soil, air and water). In addition to the detection limit, the following data was extracted from the studies to help calculate the environmental detection limit.

> *Soil*- sample volume, sample concentration, extraction volume, volume added to the reaction, and total reaction volume. In addition the type of soil was noted.
>
> *Air*- sampling volume, air flow rate, duration, sample concentration, extraction volume, volume added the reaction and total reaction volume.
>
> *Water*- sample volume, sample concentration, extraction volume, volume added to the reaction and total reaction volume.

For the environmental samples in these studies the sample was spiked into a matrix, filtered and extracted, or directly extracted, and detected using various detection technology. Since there are many steps in detecting environmental samples, samples may be lost in the process affecting the detection limit. Flow diagrams, similar to figure 1, were drawn for each article to asses in the calculation or the back-checking of the published environmental detection limit. After the environmental detection limit was calculated, the raw data was converted into standard units, cells per mg of soil, cells per liter of air and cells per liter of water for comparison purposes.

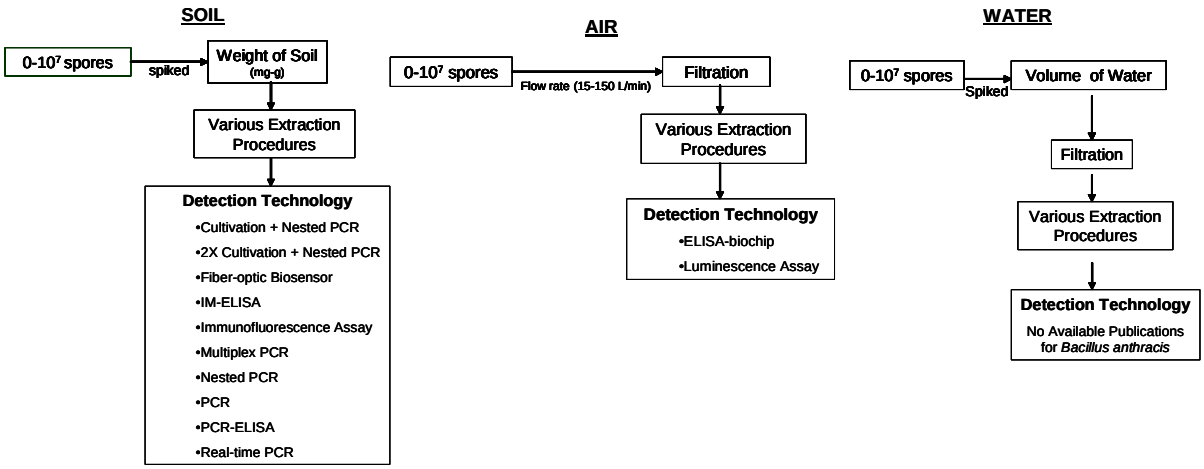

Figure 1. Flow diagrams of environmental spiked assays for soil, air, and water used to asses the environmental detection limit.

Evaluation of Detection Limit for qPCR and Plaque Assay: An experimental evaluation of the detection limit of qPCR and plaque assay using P22 and *Bacillus thuringiensis* recovered from larger surfaces. Surfaces of interest include, plastic-acrylic, wood-laminated pine, laminar, and stainless steel containing surface areas of 0.01 m^2, 0.1 m^2, and 1m^2. P22 and *Bacillus thuringiensis* are serial diluted and a total of 50 ul of the sample will be applied to the fomite in a grid formation comprised of fifty-1 □L spots. The samples are left to dry (~20 minutes) and are recovered by using the Fellowes pre-moistened surface cleaning wipes cut into 48 cm^2. Wiping is conducted by horizontal and vertical strokes across the entire surface. P22 or *Bacillus thuringiensis* are extracted from the wipe and either will be prepared for qPCR using the QIAamp DNA Mini Kit or directly used for the plaque assay. All samples with 100 PFU (or CFU) or greater the experiments will be conducted in triplicate while all sample concentrations less than 100 PFU (or CFU) will be conducted six times for each detection method.

Quantum dots (QDs) as surrogates: Quantum dots with varying properties are available commercially for various applications. Currently experimental evidence for use of QDs as surrogates of microorganisms is nonexistent but its potential as a surrogate, marker, or tracer in biodefence applications is well acknowledged. QDs have been used to detect single nucleotide polymorphisms (Xu et al., 2003), pathogens (Hahn, et al., 2005) and toxins in a multiplex manner. The work on evaluation of quantum dots as surrogates for microbial pathogens is under progress. It involves identification of characteristics of all types of quantum dots and theoretical evaluation of QDs for use as surrogate followed by an experimental validation of its usefulness. Based on the literature review the best possible method will be applied to evaluate the selected QDs as surrogates experimentally under laboratory conditions. Then the selected QD will be evaluated in field conditions. Data generation of the evaluation of QDs as suitable surrogate will be obtained through a literature review. Journal articles related to *QDs* searched on the ISI Web of Science data base using the following key words; method, QDs detection, QDs in water, QDs in air, QDs in fomite, environmental, assay, diagnostic, toxicity, surrogates for bacteria, QDs genotoxicity, QDs in biological system, QDs bacteria, QDs and DNA . The journal articles' abstracts are then exported into an EndNote file. All journal articles available on QDs used in

biological systems are under review. For the references that do pertain to QDs as surrogates a pdf copy of the article, full text, is retrieved and saved in the database. All the full text articles will be reviewed and suitable QDs and method will be determined for the experiments.

Major criteria chosen for a suitable surrogate are size, detection limit, cost, measurement techniques and toxicity.

Quantum dots (QDs) genotoxicity: Reported toxicity studies show that quantum dots induce damage to the plasma membrane, mitochondrion, and nucleus, leading to apoptosis and finally cell death. In field-scale dispersion experiments, clean-up of QD surrogates may be required (because of its toxic health effects on the workers applying it), especially if it is used at high concentrations. As per earlier reports on QD toxicity and literature review we have chosen CdSe/ZnS quantum dots (amine functional group, EviTags, Evident Technologies (http://www.evidenttech.com) for the genotoxicity study as this can also be used further in surrogate studies. Since there is no report on genotoxicity of quantum dots in any living system, we evaluated DNA damage due to CdSe quantum dots under *in vitro* conditions on human lymphocytes using single cell gel electrophoresis assay (Comet assay).

Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

Instrument detection limits of various methods for Bacillus anthracis were documented as a distribution. In year one this same data was represented as the detection limit of *Bacillus anthracis in water*. After revisiting all of the articles in the data base, we concluded that these studies did not originate from spiked assays, therefore, had missing information that would not allow us to recalculate the environmental detection limit in water. Considering the median instrument detection limit, real-time PCR and PCR were the most rapid and sensitive methods for the detection of *B. anthracis* in solution approximately 400 and 700 cells/ml respectively; compared to Raman spectroscopy and mass spectrometry which were approximately 1.0×10^7 and 8.0×10^7 cells/ml respectively. The completed learning unit for instrument detection limit is submitted in the database with supporting documents.

There were fewer articles on the environmental (soil, air, water) detection limits of various methods for *Bacillus anthracis* than the instrument detection limit and were not documented as a distribution.

Soil: There were 7 articles on the environmental detection limit in soil. Most of the articles reported multiple detection limits because of varying the extraction method and/or optimizing a process step. The detection method with the lowest detection limit was PCR-ELISA with a detection limit of 10^2 spores/mg soil while the highest detection limit was 10^7 spores/mg of soil from the multiplex PCR detection method. Both articles differed in detection method as did they differ on the extraction method; the lowest detection limit used the Easy DNA Kit (Invitrogen) while the highest detection limit extraction method was by using a heat treatment and a 10% TritonX-100/PBS and water solution.

Air: A similar analysis for air is also complete; however, this matrix resulted with only 2 articles. Though conclusion on the detection limit cannot be made from only 2 articles, there is a trend were the efficiency of the sample collector affects the detection limit at least by 50%.

Water: The environmental detection limit in water did not produce any articles for the search that was done. There was one article on the recovery of spiked spore in finished waters and details of the article were summarized on the database.

The completed learning units for environmental detection limit in soil, air and water are submitted in the database with the supporting documents. An update of articles published in years 2006 and 2007 is to increase the data for the environmental detection limit which will provide a more comprehensive distribution. The updated learning unit is submitted as work in progress.

The work on the evaluation of the detection limit of qPCR and plaque assay using P22 and *Bacillus thuringiensis* recovered from larger surfaces has been initiated. Fellowes Premoistened Surface Cleaning Wipe 99715 was previously used for fomite studies but has been discontinued and replaced with Fellowes Premoistened Surface Cleaning Wipe 99703. To justify the use of the wipe a comparison study will be done. Preliminary experiments did produce recovery from the replacement wipe (99703) but the comparison between the two wipes recovery efficiency has not been completed. An "In progress" learning unit related to these tasks is also submitted.

The work on evaluation of quantum dots as surrogate involves identification of characteristics of all types of quantum dots and theoretical evaluation of QDs for use as surrogate followed by an experimental validation of its usefulness. Literature review suggests that it has good potential but its use as surrogate will require further evaluation and development.

Major criteria selected for a suitable surrogate are size, detection limit, cost, measurement techniques and toxicity.

The QD we have chosen to evaluate as surrogate for microorganisms is CdSe/ZnS quantum dots. But the CdSe/ZnS core shell QD (EviDot) is hydrophobic in nature thus non bioavailable, so cannot be used for DNA attachment experiments as well as toxicity tests. Then we selected CdSe/ZnS quantum dots with PEG coating and amine functional group (EviTags) which is bioavailable. The size of Evitags was claimed by manufacture ~25nm but in our primary observation under Electron microscopy resulted in ~5nm which is in the range of virus particle size. To confirm the size of QDs some other size measurement and imaging techniques will be used such as confocal microscopy. The cost of commercially available QD is very high to be used in field experiments. These QDs have been reported to be detected as single particle in *in vitro* (Dahan et al., 2003) and *in vivo* (Michalet et al., 2005) after conjugating with other biomolecules, but we did not find any available report of the detection from environmental sample or recovery of the QD from experimental environmental matrix. An "In progress" learning unit related to this task is submitted.

EviTag (QDs made of Cadmium Selenide and Zinc Sulfide) is listed as moderately toxic because of toxic effects of its components Zn, Cd, Se, and S. Since we selected EviTag as candidate for the surrogate studies due to its bioavailability and suitability for attaching DNA to it, we first assessed the toxicity potential of QDs. We evaluated DNA damage due to CdSe quantum dots under in vitro *conditions on human lymphocytes using single cell gel electrophoresis assay (Comet assay) as per standard protocols (P1Q3-SOP1v1 section 8.0). Human lymphocyte cells were treated for 3 and 6 hrs with various concentrations (0.01nM-100nM) of QDs in serum free medium and analyzed for DNA damage using Komet 5.5 software (Andor Bioimaging Systems). Three independent experiments were performed for the final results. The results showed significant DNA damage at both the treatment times. Cells treated for 6 hrs also have shown significantly higher DNA damage than 3hr treatment, which shows the effect of duration of*

exposure. To our knowledge, this is the first study to evaluate the genotoxicity of quantum dots in mammalian cells. A "complete" learning unit related to this task is submitted (Manuscript under preparation).

Completed units:

1. Environmental Detection Limit of *Bacillus anthracis* in Soil: LU 1166
2. Environmental Detection Limit of *Bacillus anthracis* in Air: LU 1169
3. Environmental Detection Limit of *Bacillus anthracis* in Water: LU 1171
4. Instrument Detection Limit of *Bacillus anthracis*: LU 631
5. Genotoxicity assessment of quantum dots using Comet assay: LU1202

In progress units:

1. The Evaluation of Detection Limit for qPCR and Plaque Assay Using *Bacillus thuringiensis* and P22 from Large Surface Areas: LU 1165
2. Update for years 2006-2007 for the Detection Limit of All Methods for *Bacillus anthracis*: LU 1172
3. Evaluating quantum dots (QDs) as surrogates: Activity is release, dispersion, and recovery of surrogates; Matrix is air, water, soil, or surfaces: LU 738
4. Quantum Dots as surrogates for microorganisms: LU 1203

Outputs:

8.1 Students Supported and/or Graduated: Two (one post-doc)
8.2 Publications: Two

Alok K. Pandey, Amanda B. Herzog, Joan B. Rose, Syed A. Hashsham. Potential of Quantum Dots as Surrogates for Microbial Pathogens and Evaluation of Their Genotoxicity. *107th General Meeting of the American Society for Microbiology*, Toronto, Canada, May 21-25, 2007.

Amanda B. Herzog, Alok Pandey, Tomoyuki Shibata, Joan B. Rose, and Syed A. Hashsham. Implications of Detection Limit of Various Methods of *Bacillus anthracis* in Computing Risk to Human Health. *107th General Meeting of the American Society for Microbiology*, Toronto, Canada, May 21-25, 2007.

8.3 Patents: None
8.4 Presentations: Two
8.5 Participation or organization of workshops: One
8.6 Case studies, algorithms developed: None
8.7 Human Resource Development: None
8.9 Other (consulting, interviews, etc.): None
8.10 Funds Leveraged (additional funding, resources for free): None

Outcomes (how your contributions can be used to better society):

Knowledge of the instrument and environmental detection limit of various available methods is key to the quantification of risk.

Availability of surrogates that mimic transport and dispersion of pathogens without the associated harmful health effects improves the ability to minimize risk.

Collaboration with other Projects (actual work in collaboration within and outside CAMRA):

- Data related to detection limit was used by Prof. Chuck Haas to compute and illustrate the effect of environmental detection limit in evaluating risk from a given BAC.
- LU 1165 will yield data related to recovery of smaller number of BAC surrogates from larger surfaces areas that will be used to compute the level of risk (by Prof. Patrick Gurian)

Integration with other projects (association between units in different projects):

The outcome of the units on the environmental detection limit of *Bacillus anthracis* in air, water, and soil will be used to develop algorithms that will relate detection limit to microbial risk (with team members of Drs. Joan Rose and Charles Haas)

The outcome of the unit on the evaluation of detection limit for qPCR and plaque assay using *Bacillus thuringiensis* and P22 from large surface areas will be used in research conducted by by Prof. Patrick Gurian.

Tasks for Next Year (see definition below):

Evaluation of Detection Limit for qPCR and Plaque Assay Using *Bacillus thuringiensis* and P22 from Large Surface Areas

Update for years 2006-2007 for the Detection Limit of All Methods for *Bacillus anthracis*

Evaluating detection methods for BACs selected for Year 3

Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

- Experimentally establish the environmental detection limit and effect of background (specificity) when we do use microbial surrogates (*Bacillus thuringiensis*) under field conditions. We will use both real-time PCR and 454 FLX sequencing system to evaluate both sensitivity and specificity under field conditions.

- **Tasks** are collections of research questions, problems, or hypothesis whose developments (contributions) may be described as learning units.

- Establish the real time PCR for *B. thuringiensis* and 454 sequencing system based on 16S rRNA gene.
- Prepare soil and water samples mimicking field conditions for *B. thuringiensis* spikes
- Establish recovery, detection limit, and identity in terms of sequence information focusing on *B. thuringiensis.*

References

Hahn MA, Tabb JS, Krauss TD. (2005). Detection of single bacterial pathogens with semiconductor quantum dots. *Analytical Chemistry* 77 (15): 4861-4869.

Xu HX, Sha MY, Wong EY, Uphoff J, Xu YH, Treadway JA, Truong A, O'Brien E, Asquith S, Stubbins M, Spurr NK, Lai EH, Mahoney W. (2003). Multiplexed SNP genotyping using the Qbead (TM) system: a quantum dot-encoded microsphere-based assay. *Nucleic Acids Research* 31 (8): Art. No. e43.

Dahan M, Lévi S, Luccardini C, Rostaing P, Riveau B, Triller A (2003). Diffusion dynamics of glycine receptors revealed by single-quantum dot tracking. *Science*: 302(5644):442-445.

Michalet X, Pinaud FF, Bentolila LA, Tsay JM, Doose S, Li JJ, Sundaresan G, Wu AM, Gambhir SS, Weiss S (2005). Quantum dots for live cells, in vivo imaging, and diagnostics. *Science*: 307(5709):538-544.

CAMRA OUTLINE FOR ANNUAL REPORTS

Project: II. Infectious Disease Models for Assessing Microbial Risks and Developing Control Strategies

Investigators: Joseph Eisenberg and James Koopman

Project Goals (from proposal, additional goals): Transmission Model Development (including dynamics of environmental contamination, dose-response, and behavior, as well as intra- and inter-venue transmission of pathogens)

Tasks* for Year (II): i) Developed transmission models with explicit description of environmental contamination; ii) Developed dynamic dose-response models to be integrated into transmission models; iii) Evaluated statistical models for analyzing efficacy of intervention trials; iv) Collected environmental contamination data during Influenza season to inform environmental transmission models

Research Activities (First field in learning units, starts w/ verb in -ing form, e.g., investigating):

A. Developed dynamic dose-response models and fit to experimental data (LU 1025, 1026)

B. Developed environmental infection transmission system (EITS) model (LU 1117, 1122)

C. Examined the importance of contact patterns in efficacy of interventions (LU 1186)

D. Evaluated statistical models for analyzing efficacy of intervention trials (LU 1187)

E. Collected environmental contamination data during influenza season (LU 1086)

Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

We have not entered any LU under the category type "Things I have read".

Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

LU 1025

We developed a simplistic model of the immune system to investigate the effect that time of exposure has on the risk of infection.

The model, a continuous time Markov process, describes: 1) arrival of pathogens via inoculation; 2) reproduction of pathogens; 3) arrival of immune particles; 4) natural death of immune particles; 5) death of pathogens due to the effect of immune particles; 6) death of immune particles due to the effect of pathogens; and 7) recruitment of new immune particles in the presence of pathogens

Computational experiments shows that:

1) For a given exposure, the probability of infection decreases when the time of exposure increases; e.g., the probability of infection given a dose of 100 pathogens administered over a short time (such as 1 minute), mimicking single dose exposures, is higher than the probability of

infection given the same dose administered over a longer time (such as 60 minutes).
2) Longer exposure (or inoculation) times decrease the probability of infection due to immune system activities that occur during exposure.
3) Probability of infection depends not only on the dose, but also on the timing of exposures.
These temporal dynamics are not accounted for in current empirical dose-response trials or in the dose-response models currently in use, such as the exponential and the Beta-Poisson.

LU 1026

We carried out parameter estimation of the cumulative dose model (LU 1025) for three different dose-response datasets: 1) Poliovirus type 1; 2) *Cryptosporidium parvum*; and 3) Rotavirus.

Parameter estimation was carried out by a genetic algorithm minimizing the mean square error. Statistical relevance of the parameters estimates was tested with a normal ratio likelihood test. We compared these results to those obtained with the exponential and the Beta-Poisson dose-response model.

For Poliovirus and *Cryptosporidium parvum* the dose-response curve produced by the cumulative dose model was statistically significant. In addition, the mean square error is smaller than the best fit of the exponential model.

For rotavirus the results of the parameter estimation were not statistically significant. Both the cumulative dose model and the exponential model do not pass the normal ratio likelihood test. Therefore, they are not good models for the data. This fact was already known for the exponential model. Rotavirus dataset, however, can be fitted by using the Beta-Poisson model. This is due to the heterogeneity in the susceptibility to infection. Unlike the Beta-Poisson model, the cumulative dose model does not incorporate heterogeneity in the susceptibility to infection. Further work is needed to extend the cumulative dose model to incorporate heterogeneity in susceptibility to infection (LU 1024).

Since we are here only evaluating the model using single exposure trial data we have no information on the temporal dynamic parameters of the model. Therefore, the model is not completely identifiable; i.e., there are many possible configurations of parameters of the cumulative dose model that produce statistically significant results. Data from dosing trials with multiple doses and different times of exposure is needed to further inform our dynamic dose response model.

The detailed results of this work can be found in chapter 3 of the document attached in the LU 1025.

LU 1117

We developed an environmental infection transmission system (EITS) compartmental model based on ordinary differential equations. In this model populations are divided into one of three homogeneous compartments: susceptible (S), infectious (I) and removed (R). We include the following two behavioral interactions between the population and the environment: individuals pick up and deposit pathogens from and to the physical environment. A literature review was conducted to obtain information on disease natural history, dose-response rate, pickup rate, deposit rate, pathogen survivability.

The basic reproductive number, R_0, is the product of three terms: the total pathogens deposited by an infectious individual during his infection period, the proportion of viable pathogens picked up by individuals from environment, and pathogen infectivity.

This new EITS model relaxes the instantaneous contact assumption of the traditional susceptible-infectious-removed (SIR) model. Comparing these two model structures, we observe that the EITS model slows down the dynamics of infection transmission but ends at the same cumulative infection comparing to classic SIR model

LU 1122

We converted the deterministic EITS model presented in LU 1117 to a stochastic realization (using the Gillespie event algorithm). In this new model we observe some effects that can not be observed in the deterministic model. For example, the same configuration of a stochastic model can have a wide range of results from extinction of the infection to large outbreaks. The deterministic compartmental model, on the other hand, only shows the averaged infection patterns, missing the potential variance of the infection patterns (from large outbreaks to extinction). This variance can be described as follows. When R0 < 1 and when the initial number of infectious individuals and/or the environmental contamination increases, the stochastic model results in a decrease in number of extinction events and an increase in the number of minor outbreak events. When R0 > 1 and when the number of initial infectious individuals and/or the environmental contamination increases the stochastic model leads to a decrease in extinction events and a decrease in minor outbreak events.

LU 1186

During an epidemic, infections result from a series of contacts between individuals. By holding the order in which these contacts are made, we can observe what happens when certain infectious contacts are intervened upon. There exists a subset of contacts, which if intervened upon, will cease population epidemic transmission.

This is shown by modeling contacts among individuals that generate a certain contact pattern (a series of ordered contacts between specific individuals). With this contact pattern we simulate transmission to obtain an epidemic curve (outbreak data). This simulation is repeated (keeping the contact pattern constant) with differing number of people receiving an intervention. By applying the intervention to more and more people, it becomes more difficult to generate cases. Once enough contacts are sanitized the epidemic ceases, thus there exists a threshold number. The order in which we chose individuals that will receive the intervention will change this threshold value; i.e., the threshold in which epidemic cease depends on the contact structure as much as the intervention level.

LU 1187

We simulate a dynamic stochastic nonlinear transmission model of a directly transmitted pathogen. The data (outbreak data) obtained from these simulations are then analyzed using sophisticated epidemiologic methods (hierarchical linear modeling).

We are assessing how hierarchical linear models bias the inferences made from epidemic transmission related data. We hypothesize that there exists bias in point estimates and variance estimates made from statistical analyses of nonlinear transmission models. The preliminary analysis included in this learning unit supports this hypothesis. We believe this is so, because the nonlinear transmission models deviate from the assumptions inherent in the statistical

methodology, most notably the role that chance plays in non-linear processes. Further analysis will be conducted to substantiate this finding.

Outputs:

8.1 Students Supported and/or Graduated: Ian Spicknall (PhD student), Sheng Li (PhD student), Nottasorn Pilat (PhD student), Josep M. Pujol (post-doc)

8.2 Publications:

Pujol JM, Eisenberg JNS1, Haas CN; Koopman JS. The Effect of Ongoing Exposure Dynamics in Dose Response Relationships. Submitted to PNAS.

8.3 Patents: None

8.4 Presentations:

Koopman JS, Pujol JM, Eisenberg JNS. Infection Acquisition Dynamics and Timing of Exposure Doses. Presented at the Society of Epidemiological Research (SER). 2007

8.5 Participation or organization of workshops:

8.6 Case studies, algorithms developed:

We developed algorithms for the implementation of our models. Source code is documented following the QAPP standards.

8.7 Human Resource Development:

8.9 Other (consulting, interviews, etc.):

8.10 Funds Leveraged (additional funding, resources for free):

Dr. Koopman is collaborating in the Center of Excellence in Public Health Informatics directed from the University of Utah, headed by Matt Samore, and funded by CDC. The student to be supported will be integrated into our CAMRA team.
Dr Eisenberg has an EPASTAR grant on drinking water risks associated with Norovirus exposure through distribution systems. The graduate student on this project has been integrated into the CAMRA team

Outcomes (how your contributions can be used to better society):

By modeling transmission we aim to gain a better more complete understanding of the environmental risk process. We focus the effects of realistic settings by using stochastic rather than deterministic models, by modeling both transmission and the environment, and by modeling the dynamic aspects of the dose response relationship. Our work has already shown that explicitly incorporating the environment results in slower dynamics in the epidemics than those predicted by deterministic models without the environment. Taking into account an immune-based dose-response model show us that probability of infection might depend not only on the dose but also in the time of exposure. As a result different routes of transmission have different associated risk levels. More realistic models lead to more realistic interventions. We found that the efficacy of intervention depends on the coverage as well as contact patterns between individuals.

Collaboration with other Projects (actual work in collaboration within and outside CAMRA):

A. We have collaborated with Project I to obtain data and to talk about future experiments and data collection activities. We have collaborated with Project III about our cumulative dose-response model.

B. We are collaborating with an outside research group that obtained CDC funds for the intervention trial to augment their study with environmental sampling, surveys on student movement patterns, and transmission models.

Integration with other projects (association between units in different projects):

Tasks for Next Year (see definition below):

a) Cumulative dose model with heterogeneous susceptibility to infection (LU 1024 in progress). The goal is to extend the cumulative dose model (LU 1025) to incorporate heterogeneity of susceptibility to infection. The cumulative dose model does not have a direct parameter for susceptibility. However, we believe we can achieve the same results by assuming heterogeneous parameters of the immune system.

b) Integration of cumulative dose-response into transmission models. The risk of infection given a dose of pathogens might strongly depend on the route of transmission (LU 1164 in progress). In this work we aim to integrate the cumulative dose model (LU 1025) into transmission systems.

c) Environmental sampling during influenza season of winter 2007/2008 in the university residential halls setting (LU 1086). Environmental sampling will be conducted in the common areas of 7 residential halls (computer room, lounge, and cafeteria) as well as in dorm rooms of students with self-report influenza-like symptoms and those with no symptoms. Sampling will be divided to commonly touched and uncommonly touched areas.

d) The role of environmental contamination in point source norovirus outbreaks and subsequent secondary spread into households within the state of Michigan (LU 1087). This study will be conducted in collaboration with the routine outbreak investigation unit within the Michigan Department of Communicable Health (MDCH) and the appropriate local health department (LHD). Environmental samples will be collected at the site of the outbreak. For families with secondary cases, permission will be asked to take household environmental samples. Genotyping of fecal samples of the cases and the environmental samples will be performed.

e) Induced bias from improper model assumptions: a simulation study (potential LU). This learning unit extends the work introduced in LU 1187.

Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

*** Tasks** are collections of research questions, problems, or hypothesis whose developments (contributions) may be described as learning units.

CAMRA OUTLINE FOR ANNUAL REPORTS

Project: Project III Dose-Response Modeling

Investigators:

Investigator Name	Responsibilities	Project Year Started
Dr. Charles N. Haas	***Project Manager:*** Guidance of the overall direction of the literature review process in which Project III will gain the data necessary for work performed. Judging the applicability of the data gained through literature review as well as guiding the development of new models.	First Year
Dr. Timothy A. Bartrand	***Primary Data User:*** Searching out and determining the general applicability of currently available dose-response data. Assisting other personnel in searching out dose-response data. ***Advanced Dose Response Modeler:*** Initiate investigations into development of advanced dose-response modeling. ***Exposure Assessment Modeler:*** Initiate investigations into development of exposure to pathogenic microorganisms and inclusion into dose-response modeling	First Year
Mr. Mark H. Weir	***Primary Data User:*** Searching out and determining the general applicability of currently available dose-response data. Assisting other personnel in searching out dose-response data. ***Advanced Dose Response Modeler:*** Initiate investigations into development of advanced dose-response modeling. ***Project IIII Quality Assurance Manager:*** Write and maintain Quality Assurance Project Plan and standard operating procedures for Project III personnel, and quality of data and information generated from Project III	First Year
Mr. Sushil Tamrakar	***Primary Data User:*** Searching out and determining the general applicability of currently available dose-response data.	Second Year
Mr. Yin Huang	***Primary Data User:*** Searching out and determining the general applicability of currently available dose-response data.	Second Year

Project Goals (from proposal, additional goals):

Validated dose response relationship are necessary components of both static and dynamic risk assessment. Project III is intended to comprehensively review available experimental dose response data from the open literature and develop and validate dose response models for bioterrorism agents and other agents of concern. During the first two years of CAMRA, dose response models will be based primarily upon experimental data found in the literature. In subsequent years, "next generation" dose response models will be developed using other data such as epidemiological data and based on theoretical considerations. The dose response models developed in project III will contribute to quick decision making in the event of an attack or outbreak and use of risk for evaluating alternatives for cleanup after attacks or outbreaks.

Tasks* for Year (I):

Continue literature review for Category B agents as well as Category A agents where complete amounts of data have not yet been found.

Begin literature review process for validation data. The primary data source for validation will be epidemiological studies. Validation will be performed first for those microorganisms in which there are complete or nearly complete dose response models.

Continue development of theoretical (mechanistic) dose response models. These models will provide dose-response characteristics for organisms for which dose-response data are not available, for subgroups whose response may vary from the overall population (e.g., diabetic individuals) and will enable investigation of physiological and microbial processes associated with infection and transmission. Validation data in the form of in vivo and in vitro microbial growth rates and time-to-infection, time-to-death data will be collected and analyzed as a component of this task.

Research Activities (First field in learning units, starts w/ verb in -ing form, e.g., investigating):

Dose response modeling, advanced dose response modeling, exposure modeling

Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

Microorganism or Disease or Research Task	**In Progress Learning Unit**	**Completed Learning Unit**
Category A		
Variola major dose-response	719	Not considered completed to date
Variola major age dependency	1175	1179
Yersinia pestis	Currently being written	1100
Ebola	1014	1007
Marburg	1014	1007
Lassa	983	985
Francisella tularensis	Currently being written	1102
Category B		
Coxiella burnetii	1142	Not written yet
Burkholderia pseudomallei	1006	Not written yet
Category C		
XDR (Drug resistant TB)	Currently being written	1102
Development of Mechanistic Dose-Response Models		
Microbial growth kinetics	1105	Currently being written

Outputs:

8.1 Students Supported and/or Graduated:

Student Name	Position Title	Responsibilities
Dr. Timothy A. Bartrand (*)	Post Doctoral	***Primary Data User***: Searching out and determining the general applicability of currently available dose-response data. Assisting other personnel in searching out dose-response data. ***Advanced Dose Response Modeler***: Initiate investigations into development of advanced dose-response modeling. ***Exposure Assessment Modeler***: Initiate investigations into development of exposure to pathogenic microorganisms and inclusion into dose-response modeling.
Mr. Sushil Tamrakar	PhD Student	***Primary Data User***: Searching out and determining the general applicability of currently available dose-response data.
Mr. Yin Huang	PhD Student	***Primary Data User***: Searching out and determining the general applicability of currently available dose-response data.
(*) Partial		

8.2 Publications:

Microorganism or Disease	Publication Title	Journal	Publication Status
Bacillus anthracis	Dose-Response Models for Inhalation of *Bacillus anthracis* Spores: Interspecies Comparisons.	Risk Analysis	Currently under Review
Variola major	Quantification of the Effects of Age on Dose Response of *Variola major* in Suckling Mice	Risk Analysis	Currently under Review
Lassa Fever	Dose Response Model for Lassa Virus	International Journal of Human Ecology & Risk Assessment	Currently under Review

8.3 Patents:

Not Applicable

8.4 Presentations:

Microorganism or Disease	Presentation Title	Presentation Audience
Bacillus anthracis	Effect of Host Species on the Dose-Response of Inhaled *Bacillus anthracis* Spores.; Mark H. Weir, Charles N. Haas, Timothy A. Bartrand.	DHS University Network Summit on Research and Education (Poster)
	Effect of Host Species on the Dose-Response of Inhaled *Bacillus anthracis* Spores.; Mark H. Weir, Charles N. Haas, Timothy A. Bartrand.	Drexel University Research Day (Poster)
	Effect of Host Species on the Dose-Response of Inhaled *Bacillus anthracis* Spores.; Mark H. Weir, Charles N. Haas, Timothy A. Bartrand.	First Annual Drexel University Research Symposium
Variola major	Quantification of the Effect of Host Age on Dose-Response of *Variola major* in Suckling Mice.; Mark H. Weir, Charles N. Haas.	2007 SRA Annual Meeting

Yersinia pestis	Dose Response Modeling of *Yersinia pestis* (Plague Causitive Organism) Reveals High Levels of Dispersion.; Bartrand, T.A., Kurugatta, B.B., Haas, C.N	DHS University Network Summit on Research and Education (Poster)
	Dose Response Modeling of Yersinia pestis (Plague Causitive Organism) Reveals High Levels of Dispersion.; Bartrand, T.A., Kurugatta, B.B., Haas, C.N.	Drexel University Research Day (Poster)
Francisella Tularensis	The Application of Food Microbial Growth Models to in-vivo Frencisella tularensis Growth in Laboratory Animals.; William McGarry, Timothy A. Bartrand, Charles N. Haas.	Drexel REU Student Poster Sessions

8.5 Participation or organization of workshops:

Association / Society Name	Conference / Symposium Title	Workshop Title	Location	Date	Instructors
International Water Association	14th International Symposium on Health-Related Water Microorganisms	Introduction to Quantitative Microbiology	Tokyo, Japan	9 September 2007	Dr. Joan B. Rose Dr. Charles N. Haas Dr. Charles P. Gerba Dr. Yoshifumi Masago Dr. Tomoyuki Shibata
American Society of Microbiology	107th General Meeting *Workshop Session*	WS-10 Quantitative Microbial Risk Assessment (QMRA)	Toronto Ontario, CA	20 May 2007	Dr. Joan B. Rose Dr. Charles N. Haas Dr. Syed A. Hashshram Dr. Charles P. Gerba Dr. Yoshifumi Masago Dr. Tomoyuki Shibata

8.6 Case studies, algorithms developed:

Timothy A Bartrand working as a post-doctoral student has written a routine for developing mechanistic dose-response models using stochastic in vivo birth and death models for infectious organisms. The routine is written as an R source code and has been distributed to project III personnel and archived. In the first quarter of 2007/2008, the code will be used to predict growth rates and infection by *Francisella tularensis* and will use in vivo growth rate models developed by William McGarry for CAMRA during 2006/2007.

From a literature review of *Variola major* it was found that the dose-response characteristics depended on host age. From this point the original R source code performing the maximum likelihood estimation (MLE) used to determine the best fitting dose response models was enhanced to allow age dependency to be included into the dose response models. Mr. Weir showed that modified versions of the beta Poisson and exponential models provided a significant improvement in fit.

8.7 Human Resource Development:

Year two saw the addition of a new investigator by bringing Mr. Yin Huang on as a PhD student. Mr. Huang immediately began work by searching for dose-response data for *Yersinia pestis* as well as *Burkholderia pseudomallei* epidemiological data from China which may need to be translated from Chinese for validation of dose-response models.

8.9 Other (consulting, interviews, etc.):
Not Applicable.

8.10 Funds Leveraged (additional funding, resources for free):

Student Name	Position Title / Funding Source	Responsibilities
Mr. Mark H. Weir	PhD. Student External funding: Department of Education: Graduate Assistantships in Areas of National Need (GAANN) Fellowship	***Primary Data User***: Searching out and determining the general applicability of currently available dose-response data. Assisting other personnel in searching out dose-response data. ***Advanced Dose Response Modeler***: Initiate investigations into development of advanced dose-response modeling. ***Project III Quality Assurance Manager***: Write and maintain Quality Assurance Project Plan and standard operating procedures for Project III personnel, and quality of data and information generated from Project III.
Mr. William McGary	Visiting Undergraduate Student External Funding: Department of Homeland Security: Undergraduate Fellow	***Primary Data User***: Searching out and determining the general applicability of currently available dose-response data. ***Advanced Dose Response Modeler***: Initiate investigations into development of advanced dose-response modeling.
Mr. Andrew Lerch	Visiting Undergraduate Student External Funding: Department of Homeland Security: Undergraduate Fellow	***Primary Data User***: Searching out and determining the general applicability of currently available dose-response data. ***Exposure Assessment Modeler***: Initiate investigations into development of exposure to pathogenic microorganisms and inclusion into dose-response modeling.

Outcomes (how your contributions can be used to better society):

Bacillus anthracis:

- Reference parameter set has been generated, archived and filed. These parameters will be useful to the CAMRA community in allowing CAMRA access to the optimized parameters for *B. anthracis*. Outside of the CAMRA community, society in general can benefit from these optimized parameters mainly for protection and treatment of citizens in the event of a large scale release such as:
    - A quantified means of establishing triage for treatment of victims.
    - Suggesting decontamination levels.
    - Communicating the appropriate level of risk to the public to ensure that panic can be avoided.
    - Identify the specific risks associated to sensitive groups such as the elderly or infirmed.

Hemorrhagic Fevers:

- Reference parameter set has been generated, archived and filed. These parameters will be useful to the CAMRA community in allowing CAMRA access to the optimized parameters for Lassa virus. Outside of the CAMRA community society in general can benefit from these optimized parameters mainly for protection and treatment of citizens in the event of a large scale release. Especially for hemorrhagic fevers since there is a real and serious threat of secondary transmission the large scale release may not be the largest threat to national security and health of the citizenry.
    - Cordoning off a "control" or "quarantine" zone to reduce the spread of the disease through secondary transmission and exposure.
    - A quantified means of establishing triage for treatment of victims.
    - Suggesting decontamination levels.
    - Communicating the appropriate level of risk to the public to ensure that a panic can be avoided.
    - Identify the specific risks associated to sensitive groups such as the elderly or infirmed.

Francisella tularensis:

- Developed approach to modeling incubation of *F. tularensis* in mouse organs. This result identified classes of dose response models which predicted microbial growth and provided more appropriate sub-models for development of mechanistic dose response algorithms. These kinetic models are an advancement on the traditional ones used for in-vivo growth and can aid in determining when to commence treatment of the disease and how aggressively to prosecute that campaign.

Variola major:

- First quantification of the effect of age dependency on dose response models. It has been known clinically that different age groups will react with varying levels of severity when infected with *V. major*. This result marks the first quantification of the effect that age has on dose response models allowing for the modeling of this age dependency directly into the dose response models. The more robust and descriptive the dose response models are to how the infection acts on the host the benefits to risk estimation and decision making process are obvious.

Collaboration with other Projects (actual work in collaboration within and outside CAMRA):

In order to perform the development of mechanistic dose response models Project II will be contacted for information and data that is pertinent to the mechanisms of human physiology and dose accumulation. These data will be used in development of dose response models that are more appropriate for use in disease transmission modeling.

In order to complete the presentation for XDR (drug resistant tuberculosis) CAMRA Projects I and III worked together when the emerging issue of secondary exposure on airlines. This collaborative work cumulated in the afore mentioned presentation to the DHS Chief Medical Officer Dr. Jeff Runge.

Integration with other projects (association between units in different projects):

Each of the learning units that are entered for dose-response modeling has a connection to Project IV to assist in their work by determining how well the dose-response models will estimate risk to humans.

Tasks for Next Year (see definition below):

Progress through more developments of mechanistic dose response models.

Three microbial kinetics models will be further refined and included into dose response models. Microbial growth rate data will be used to develop realistic relations for in vivo growth and death. Output from the growth model will be used to predict the probability of infection associated with a given initial microbial dose

Another mechanistic approach would be the start of a physiologically based advancement on dose response models. Using human physiology as a base for this mechanistic model an advancement on the current dose response model will be proposed and analyzed this coming year.

Established dose response models will be validated using available epidemiological data.

The dose response analyses performed thus far as well as being performed currently will be used to make reference parameter sets such as that made for inhalation of *Bacillus anthracis.*

Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

Further dose R source codes will be written and validated since R is the preferred language to program in and perform analysis with. Especially for the mechanistic dose response models that will be developed new R codes will of course be written as well as other languages that may be found to be useful to the modeling that needs to be done.

Reference parameter sets will be developed for Category A agents since all these microorganisms have dose response models associated with them or are in the process of being completed now.

* **Tasks** are collections of research questions, problems, or hypothesis whose developments (contributions) may be described as learning units.

CAMRA OUTLINE FOR ANNUAL REPORTS

Project: Project III: Conduct of Animal Experiments to Determine the Dose Response of Mice following Oral Exposure to *Francisella tularensis* Type A

Investigators: Bolin, CA and Haas, C

Project Goals (from proposal, additional goals): Dose-response curve(s) for infection and death related to oral challenge with *Francisella tularensis* in mice

Tasks* for Year (II):

Estimate of dose response to oral challenge with *F. tularensis* and selection of virulent challenge strain.

Final dose-response curve for infection and death related to oral challenge with *F. tularensis*.

Research Activities (First field in learning units, starts w/ verb in -ing form, e.g., investigating): Modeling dose-response

Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

in progress unit 871

Outputs: None at this time

Outcomes (how your contributions can be used to better society): None at this time.

Collaboration with other Projects (actual work in collaboration within and outside CAMRA): None at this time

Integration with other projects (association between units in different projects):

Tasks for Next Year (see definition below): Complete the studies that were supposed to be done in Year 2 but had to be delayed due to enhance biosafety requirements and animal care and use approvals. We will also anticipate an additional set of experiments with either multiple doses of *F. tularensis* over time or move on to another agent. These experiments will have to be planned in collaboration with other personnel on Project III and Project II.

Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

* **Tasks** are collections of research questions, problems, or hypothesis whose developments (contributions) may be described as learning units.

CAMRA OUTLINE FOR ANNUAL REPORTS

Project: Project IV Drexel

Investigators: Patrick Gurian

Project Goals (from proposal, additional goals):

Use a scenario-based approach to identify key decision points and uncertainties in bioterrorism risk management plans.

Develop statistical descriptions of uncertainty in model parameters

Identify promising strategies to reduce uncertainty and manage bioterrorism risk.

Tasks* for Year (II):

Core:

Develop a compartment model of the fate and transport of *B. anthracis* in a building

Develop a Bayesian hierarchical model of *B. anthracis* dose-response that describes interspecies variability in dose-response model parameters

Additional:

Work with Chris Choi's group on water distribution scenario. Evaluate neighborhood-level disinfection as a strategy to provide drinking water after the contamination of a water distribution system.

Work with Liz Casman to identify appropriate topic for Mental Models interviews

Research Activities (First field in learning units, starts w/ verb in -ing form, e.g., investigating):

1) Fitting a Bayesian hierarchical dose-response model

2) Developing a mass-balance compartment model to predict surface concentration and risk after a release of *B. anthracis*.

Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

Dose-response data provided by Project III has provided essential information for the hierarchical model of interspecies dose-response variability.

A compartment model of B anthracis fate and transport developed by Sextro and collaborators has provided a basis for relating environmental sampling results to human health risk.

Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

Unit 1063 identifies contamination of water provided by a neighborhood treatment unit during transport and storage as a concern. This can inform the development of post-event response plans which may require neighborhood-level disinfection units.

A functioning compartment model for *B. anthracis* fate and transport has been developed and will be used to provide guidance to building sampling and re-opening efforts.

Preliminary estimate of interspecies variability of *B. anthracis* dose-response parameters have been developed which will be used to develop a safety factor for interspecies extrapolation.

Outputs:

8.1 Students Supported and/or Graduated:

Graduated: Nicholas Dudley Ward, M.S. June, 2007
Supported: Jade Mitchell-Blackwood

8.2 Publications:

"Evaluation of Neighborhood Treatment Systems for Potable Water Supply," Verónica Corella-Barud, Kristina D. Mena, Shawn G. Gibbs, Patrick L. Gurian, and Alberto Barud, submitted to *International Journal of Environmental Health Research*.

"Risk Perception, Risk Communication, and Risk Management," Patrick Gurian. *Quantitative Microbial Risk Assessment Institute Handbook*, Michigan State University, August 2007.

"Statistics and Uncertainty" Patrick Gurian, *Quantitative Microbial Risk Assessment Institute Handbook*, Michigan State University, August 2007.

8.3 Patents: None

8.4 Presentations:

Gurian, Dudley Ward, and Kenyon. "Responding to anthrax contamination: Listening to surfaces and talking to people," Society for Risk Analysis Annual Meeting, December 2006.

Jade Mitchell-Blackwood, J., P.L. Gurian, and M. Weir. "A Bacillus Anthracis Dose Response Model" Ninth Annual Research Day at Drexel University, Philadelphia, PA (April 17th, 2007).

Accepted for Dec. 2007 Society for Risk Analysis Meeting:
Mitchell-Blackwood J., P. Gurian, M. Weir, "A Bayesian statistical modeling approach for *Bacillus anthracis* dose-response data".

8.5 Participation or organization of workshops:

Gurian, P.L. "Risk Characterization" presented at Quantitative Microbial Risk Assessment (QMRA) Workshop, 107th American Society for Microbiology General Meeting, May 2007, Toronto, Canada.

8.6 Case studies, algorithms developed:

R-language code to fit Bayesian hierarchical dose-response models has been developed and is being validated. Matlab code to model the fate and transport of B. anthracis in buildings has been written and is being validated.

8.7 Human Resource Development:

One M.S. student, Nick Dudley Ward graduated. Jade Blackwood, a doctoral student, attended the QMRA Institute and is being trained in Bayesian hierarchical model fitting.

8.9 Other (consulting, interviews, etc.): NA

8.10 Funds Leveraged (additional funding, resources for free):

Jade Blackwood obtained a GAANN fellowship for the 2007-2008 academic year. This provides $22,600 in stipend and $12,224 in tuition. A grant for $490,000 to establish a fellowship program in microbial risk assessment was obtained from The Department of Homeland Security.

Outcomes (how your contributions can be used to better society):

Understanding the relationship between environmental sampling and risk may help provide guidance to clean up efforts after a microbial contamination event.

Understanding the extent of interspecies variability in dose-response models may help interpret studies involving surrogate species. For example, it can inform the estimation of an appropriate interspecies safety factor.

Collaboration with other Projects (actual work in collaboration within and outside CAMRA):

I have reviewed the expert model developed by Liz Casman at Carnegie Mellon. This will inform the development of an interview protocol for the Mental Models study.

I have worked with Chris Choi to develop an appropriate water release scenario and associated policy questions.

Integration with other projects (association between units in different projects):

Dose-response data from Project III is being used to develop Bayesian hierarchical dose-response models.

Tasks for Next Year (see definition below):

Core Tasks

Complete validation of compartment model and verify correspondence between environmental surface concentrations and human risk

Complete validation of dose-response hierarchical model and explore an additional pathogen, probably tularemia. Explore a new framework in which the dose-response parameters for different species are modeled as deriving from correlated distributions, rather than from a single distribution.

Extend *B. anthracis* scenario to include costs and benefits of alternative risk-based standards for microbial contamination

Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

It is anticipated that estimates of interspecies variability in *B. anthracis* dose-response model parameters should be available in the next year, and that an example calculation of how this can be used to develop an interspecies extrapolation safety factor will be completed. Tables relating environmental sampling results to risk and recommending minimum surface sampling areas to clear sites will also be developed in the coming year.

* **Tasks** are collections of research questions, problems, or hypothesis whose developments (contributions) may be described as learning units.

Project IV: Assessment-Analysis Interface, CMU: Public Perception of Bioterror Risks

Investigators: Patrick Gurian, Elizabeth Casman, Mitchell Small, Julie Downs

Project Goals (from proposal, additional goals):

APG: Develop an integrated decision model to understand bioterrorism/pandemic impacts, assess uncertainties, and prioritize CAMRA specific research efforts
APM: Integrated decision tool that links exposure (Project I), infectious disease modeling (Project II), and dose-response (Project III) to social factors
Outcome: Practical guidance to inform risk management decisions that must be made in preparation for and in response to bioterrorist/pandemic events

Tasks* for Year (II):

Development of the Expert Model and Influence Diagram for pandemic flu scenario
Internal CAMRA and EPA/DHS reviews of expert model
Identification of affected population sectors
Identification of critical decisions and choices
Survey protocol development
CMU and MSU IRB and EPA approval of protocol
Training of interviewers
Pilot test of protocol
Recruitment of subjects
Semi-structured interviews
Transcription and coding of interviews

Research Activities (First field in learning units, starts w/ verb in -ing form, e.g., investigating):

LU 576 Designing and conducting mental models study

LU 868 Flu transmission mental models project

LU 1010 Creating influence diagram of influenza transmission

LU 1031 Developing interview protocol

Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

LU 572 contains document with this information.

Also see the file attached to LU1010 (diagram documentation).

Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

in progress unit 576, completed items 1-8 of 11 tasks.
in progress unit 1010, feedback obtained from Drs Koopman & Gurian.

Outputs:

8.1 Students Supported and/or Graduated: 1 supported
8.2 Publications: one still in revision; reviews were favorable but paper too long.
8.3 Patents: 0
8.4 Presentations:

- Casman, E. and Fischhoff, B. Risk Communication Planning for Dynamic Situations: the aftermath of a plague bio bio-attack, DHS Summit on Research and Education), Washington, DC, March 15-6, 2007.
- Casman, E. Public Communication Needs for Plague Bioterrorism Incidents. Society for Risk Analysis (SRA) Annual Meeting, Baltimore, Maryland December 3-6, 2006.

8.5 Participation or organization of workshops:
DHS Summit on Research & Education March 2007
CAMRA 2007 All-PI Meeting February 2007
8.6 Case studies, algorithms developed: Mathematical model of plague stability in urban rodent populations
8.7 Human Resource Development: ?
8.9 Other (consulting, interviews, etc.): 0
8.10 Funds Leveraged (additional funding, resources for free):
NSF Grant SES-0433152 for plague risk communication
CMU Dean's fellowship for student (plague transmission dynamics)
NSF fellowship for student
Subcontract from CREATE to study pandemic flu economics

Outcomes (how your contributions can be used to better society):

The method developed for preparing risk communication content should help communicators deliver messages containing all the important concepts for dynamic and/or complicated risk situations. (paper in revision)

The plague dynamics model can be used to evaluate the ability of plague to become established in urban rodent populations. Data that is routinely collected: flea index and rat carrying capacity, are used to locate the ecosystem in a phase diagram with regions of plague stability and plague burn-out. (This work will be presented at the December 2007 Society of Risk Analysis Meeting. It has already been awarded the best student paper in ecology award.)

Collaboration with other Projects (actual work in collaboration within and outside CAMRA):

Collaborating with Lester Lave (CREATE) on a study of the economic implications of pandemic flu.

Integration with other projects (association between units in different projects):

To complement Project 2's study of flu transmission, we changed scenarios for our public perception project from an anthrax attack to influenza transmission. PIs from Project 2 have reviewed the influence diagram developed for this project.

Tasks for Next Year (see definition below):

Pilot test of protocol (ongoing)
Recruitment of subjects
Semi-structured interviews
Transcription and coding of interviews
Analysis of data
Conduct web survey based on results
Analysis of survey
Report findings

Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

The interviews should reveal attitudes and concepts regarding how people get and avoid getting the flu. The survey will help us determine the prevalence of these attitudes. This information is of interest because peoples' knowledge and attitudes shape their behaviors. If concepts are discovered that lead to self-defeating infection-avoidance strategies, they can then be targeted for correction with educational materials.

* **Tasks** are collections of research questions, problems, or hypothesis whose developments (contributions) may be described as learning units.

Project V. WEBER CAMRA OUTLINE FOR ANNUAL REPORTS

1. Project: V, Knowledge Management, Transfer, and Learning

2. Investigators: Rosina Weber (PI), Michael Atwood (Co-Investigator), Sidath D. Gunawardena (funded RA), Marcia Morelli (unfunded doctoral student)

3. Project Goals (from proposal, additional goals):

Our primary goal was to build the web-based knowledge repository to support sharing and leveraging for the CAMRA community members. The system is in operation since July 20, 2006 in its version 1.0. The concept of an evolving learning unit refers to adapting the repository main artifact to the needs and culture of this community. As a result of work in Year 1, the learning unit and the system has evolved in many aspects requiring the design of a totally renewed Version 2.0. The design is almost finished, pending some few details in the reporting and visualizations. The implementation is ongoing, with testing planned to start in November and Beta testing at the 2008 CAMRA ALL PI MEETING. The IRB for the survey was recently approved and the first round will be mailed in November to all members. In Year III, we will conduct a usability test after Version 2.0 is launched and the respective IRB approved by MSU and EPA.

A major distinction in our plans from the original proposal is a swap of activities from Year III to Year IV. The work on the data warehouse was postpones to Year IV while we use Year III to complete the work in the knowledge repository.

4. Tasks* for Year (II):
Revising Learning Units
Building Version 2.0 of Knowledge Repository
Defining Domain Structure for QMRA
Applying Reasoning Methods on the Knowledge Repository

5. Research Activities (First field in learning units, starts w/ verb in -ing form, e.g., investigating):
In this period, investigators from Project V have focused their efforts on designing and developing version 2.0 of the Knowledge Repository (KR). This was done is parallel with maintaining the existing KR.

1. Revising Learning Units
2. Revising Review Process
3. Designing CAMRA KR
4. Assessing similarity (verbs, algorithm for taxonomy, testing trigram)
5. Implementing CAMRA KR
6. Building taxonomy
7. Creating a movie (accomplishment unit status in progress)

6. Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

Things I have read Learning Unit number 1195
Assessing similarity between text strings using trigrams can be designed in different ways to increase accuracy in comparisons (Burkhardt and Kärkkäinen 2002).
Things I have read Learning Unit number 1205

The DICE coefficient is a useful metric for comparing the results of trigrams in string comparison (Kondrak 2005).

7. Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

7.1. Revising Learning Units (1209 1210; 1207, 1208; 1072, 1073)

7.1.1 Revising Learning Units (Research Activity Field) (1209 1210)
Things that are in progress Number 1209 and Things I have completed 1210
When Revising learning units we wanted to find out how to reduce the frequency of users entering overly long, or overly specific entries in the research activity field.
Experimental Design was as follows:
Examine existing research activity field entries;
Determine common errors;
Determine how to restructure the research activity field to reduce errors.
Contribution:
We learned that it was necessary to provide constant guidance to users when entering research activities, which we implemented through designing a pull down menu that constrains the entry to only one research activity and offers choices of research activity verbs and nouns for users to select. We kept the ability to enter a new research activity verb or noun as needed by the users.
Results:
We found that research activities were too specific and users were having difficulty entering a general research activity. Sometimes, due to lack of guidance, they would enter multiple research activities rather than only one as required.

7.1.2 Revising Learning Unit field structure (Impact Field) (1207, 1208)
Things that are in progress Number 1207 and Things I have completed 1208
When revising learning units we wanted to find out whether the learning units needed new fields.
Experimental Design was as follows:
Obtain feedback from CAMRA community members and funding agencies as to any additional fields to incorporate into the existing learning unit structure.
Contribution:
Adding a new field "Impact" to document the impact of the research can demonstrate how the findings of that unit can help achieve the overall goals of CAMRA.
Results:
CAMRA uses the Kellogg Foundation Logic Model as part of its evaluation process. This model requires the capturing of the impact of the research, i.e. how it brings CAMRA closer to achieving its goals.

7.1.3 Revising Learning Unit field structure (1072, 1073)
Things that are in progress Number 1072 and Things I have completed 1073

When Revising learning units we wanted to find out whether changes are needed in the design for the learning unit structure and individual elements.
Experimental Design was as follows:
Obtaining feedback from CAMRA members, holding meetings to discuss suggested changes with HCI experts, estimating requirements for revisions for Version 2.
Contribution:

Splitting the contexts field into two sub-fields: domain specific contexts and general contexts can aid the search to utilize distinct methods for those contexts of distinct nature.
Results:
While designing the search function for retrieving learning units, we determined that elements in the field designated for contexts can be of two nature: domain specific or domain independent. We learned that different methods would be required for each type of context elements.

7.2. Revising Review Process (1075, 1077)

Things that are in progress Number 1075 and Things I have completed 1077
When revising the review process we wanted to find out what improvements to the review process to implement to benefit the CAMRA community.
Experimental Design was as follows:
Obtaining feedback from CAMRA members and holding meetings to discuss suggested changes with HCI experts.
Contribution:
A commenting interface can be used as a medium for the reviews as well as other user comments as long as the visibility of the comments is determined by the role of the user. This allows the units to be made visible to the community upon submission for review.
Results:
CAMRA members wanted units to be available to the CAMRA community the moment they were submitted for review. They suggested a blog type interface to facilitate the interchange of ideas and the development of the community. They also requested a way that units could be shown to the advisors before submission and a way where advisors could make comments.

7.3. Building taxonomy (1082, 1083)

Things that are in progress Number 1082 and Things I have completed 1083
When assessing similarity we wanted to find out a taxonomy of terms used by CAMRA members in the learning units to represent the QMRA domain.
Experimental Design was as follows:
We analyzed the terms in the Research Activity and Contexts fields to gather terms with which to build taxonomies for the QMRA domain that can be used in these two fields.
Contribution:
From the analysis of the units, the relationships between the nouns in the Research Activity field and the terms in the Contexts field allowed for the terms to be hierarchically organized in a structure - a taxonomy. The overall diversity of the terms required several taxonomies to be created.
Results:
For the purposes of assessing similarity between units, the taxonomy should include nouns describing entities and methods (the non-verb portion of Research Activity and Contexts), while verbs can be organized in a separate structure.
The taxonomy to represent terms in the QMRA domain from learning units is not all encompassing and has to be coded such that it is able to grow along with the knowledge repository.

7.4. Designing CAMRA KR (1189)

Things that are in progress Number 1189
While designing the CAMRA Knowledge Repository, we are trying to find out the final design for the CAMRA knowledge repository within CAMRA project period until 2010.
Experimental Design:

Design version 2.0 of the knowledge repository based on
- feedback from CAMRA members of their experiences
- feedback from funding agencies
- recommendations from HCI experts;
The design will be composed of sub-tasks:
- design learning units interface and submission
- design LU review process
- design accomplishment units
- design search and browsing
- design reporting
- design visualizations

7.5. Assessing similarity (1084, 1085; 1191, 1192; 1193)

7.5.1 Assessing similarity between Research Activity Verbs (1084, 1085)

Things that are in progress Number 1084 and Things I have completed 1085
When assessing similarity we wanted to find out how to assess the lexical similarity between all the verbs used in the research activity field to facilitate the similarity assessment between learning units for retrieving similar units in search design.
Experimental Design was as follows:

- List all verbs used in learning units to describe research activities.
- Understand their affinities and research about their categories from a linguistic perspective.
- Determine the relative similarity between verbs for the purposes of assessing similarity between research activities.
- Create a cross table that represents the lexical similarity between all the verbs to represent their relative similarity with numbers.

Contribution:
Different verbs were used in learning units that belong to a unique linguistic category of verbs, suggesting that they are highly similar for the purposes of comparing learning units, even when they are not synonyms.
A cross table identifying the similarity between the research activity verbs was created. Terms are scored with respect to each other on a scale of 0...1, where 1 denotes synonyms and 0 denotes verbs with no similarity. The cross table is not exhaustive and will have to be updated as more units are created.
Results:
The way to assess the lexical similarity between verbs used in the research activity field is provided by a table that represents the similarity between learning units for retrieving similar units in search design.

7.5.2 Comparing similarity metrics (1191, 1192)

Things that are in progress Number 1191 and Things I have completed 1192
When comparing methods for similarity assessment, we are trying to decide between the Trigrams with the Dice Coefficient and Damerau Levenshtein Distance metrics: which metric should be used to determine if a typo has been made, and which should be used to find similar words, and which thresholds should be adopted.
Experimental design:
A set of 650 words will be assigned random typos. The two methods will be evaluated:
1. Typos are compared to Words and expressions found in learning units from Year 1 using the Damerau Levenshtein Distance;

2. Typos and words in learning units from Year 1 are converted into trigrams and compared with the Dice coefficient;
The results will be compared and the absolute numbers will be studied to identify thresholds when each of the methods is used.
The method with more consistency in identifying a typo as such as demonstrated by statistical measures will be selected. We will also be seeking to identify the most consistent and reliable method to identify a similar word or expression.
Contribution:
Similarity
From the analysis of the attached table, the use of gapped trigrams and the dice coefficient has the longest distance between averages of similar and dissimilar words. The standard deviation is smaller when no trigrams are used, but this comes with the shortest distance between average of similar and not similar words. It is also when gapped trigrams are used that the maximum value of result found in not similar words is smaller than the minimum value obtained when comparing two similar words. For this reason, to compare words to assess similarity, we will adopt the gapped trigram with the Dice coefficient. The threshold to be used will be 0.45
Typos
We excluded the gapped method for difference in averages; we selected Edit Distance because of averages; and also because of the resulting standard deviation; selected edit for the best min; Edit is the choice.
Results:
To compare words to assess similarity, we will adopt the gapped trigram with the Dice coefficient. The threshold to be used will be 0.45
For typos, we will use the Edit distance (Damerau Levenshtein Distance. The threshold to be used will be >=0.64 will be considered a TYPO; < 0.64, a different word.

7.5.3 Algorithm for traversing domain taxonomies (1193)
Things that are in progress Number 1193
When developing an algorithm for taxonomy traversal, we are trying to design an algorithm to find similarity between domain specific terms in learning units.
Experimental Design
Determine any general rules based on taxonomy tree depth that can be used to set bounds for comparison between terms with the purpose to assess similarity between them. The result of those similarity values will be used in the assessment of similarity between learning units.
Determine any individual taxonomy specific rules based on particulars of each taxonomy that can be used to set bounds for comparison between terms.

7.6. Implementing CAMRA KR (1194)
Things that are in progress Number 1194
The ongoing implementation can be viewed by accessing the temporary link at: http://camra.ischool.drexel.edu:8080/login.jsp and type as password, “password”.

8. Outputs:

8.1 Students Supported and/or Graduated:

Sidath D. Gunawardena was supported with stipend and tuition.

8.2 Publications:

8.2.1. Weber, R. O. "Addressing Failure Factors in Knowledge Management," (2007). Electronic Journal of Knowledge Management, 5(3): pp. 333-346. Online: http://www.ejkm.com/volume-5/v5-i3/Weber.pdf

8.2.2. Weber, R. O. & Gunawardena, S. Designing Multifunctional Knowledge Management Systems. Accepted for publication in the proceedings of the Hawaii International Conference on System Sciences (HICSS-41), January 2008. (LU 1216)

8.2.3. Weber, R. O., Gunawardena, S. & Proctor, J. M. Generating Reports from Case-Based Knowledge Artifacts. In D. Wilson & G. Sutcliffe (Eds.), Proceedings of the Twentieth International Florida Artificial Intelligence Research Society Conference (FLAIRS 2007) Menlo Park CA: AAAI Press.

8.3 Patents:

8.4 Presentations:

8.5 Participation or organization of workshops:

8.6 Case studies, algorithms developed:

8.7 Human Resource Development:

8.9 Other (consulting, interviews, etc.):

8.9.1 Creating a movie (accomplishment unit status in progress)
Learning unit Number 1225, will be converted into Accomplishment Unit

8.10 Funds Leveraged (additional funding, resources for free):

8.10.1 Marcia Morelli (unfunded doctoral student) has supported human-computer interaction (HCI) efforts for Version 2.0, as part of the completion of her research experience started in Year 1, so no funds were spent on her contribution. She is a doctoral student and expert in human-computer interaction. She is the second author of one of our publications, and she is overseeing the efforts towards designing the survey and usability tests and the interactions about the IRB approvals.

8.10.2 The tuition for Sidath Gunawardena was paid through cost sharing by Drexel University.

9. Outcomes (how your contributions can be used to better society):

Unit 1210: The work describes in this unit reiterates the need for guidance to contributors during capture of learning units. In this case, we examined the field “research activities” that is meant to be a general index for the units. However, the heading for the field “What is the general research activity?” is the only information in the form and the lack of further guidance causes contributors to enter multiple activities and/or enter activities that are too specific and that would prevent a unit to be retrieved even if useful.

1208 When describing results of a research project, it is important to include the impact of each contribution. The impact refers to how the project will motivate a change in the status of a field.

1073 When designing systems, it is important to consider all functions that may be implemented to use the collected information. In the example of this unit, we learned that the contexts field should have been broken down in two to better serve the search function.

Unit 1077: The design of knowledge artifacts for a knowledge management system that includes a commenting interface can be used in the design of those systems. This design allows reviewers to revise knowledge artifacts and members to enter comments and discuss further issues, fostering collaboration between members of the community served by the system.

Unit 1083: A taxonomy of expressions from learning units that describe the QMRA domain is available for use. This can be used in further studies as it is not complete.

1085 Studies in linguistics expand the frontiers of how to use information. We learned that similarity between verbs goes beyond synonyms, and that this can be used to design a system that is more flexible to the users (because they can select multiple verbs) without compromising quality of the system's functions.

1192
It is useful to test variations of techniques in the words that are common in a domain. For the words and expression used in Year 1, we tested variations of distance metrics and ways to represent text (i.e., trigrams) and learned that the best method for assessing similarity is different from the best method to identify words that are typos.

10. Collaboration with other Projects (actual work in collaboration within and outside CAMRA):
There were no research collaborations between members of Project V and other projects.

11. Integration with other projects (association between units in different projects):
The work from Project V members as knowledge facilitators is to support members of all other projects. The approximate number of approved units in Year 2 is 70. Around 350 units were reviewed in years I and II.

12. Tasks for Next Year (see definition below): Year 3

As usually, some of these tasks may be still in-progress at the end of Year 3, with only a subset completed.

1. Complete design and implementation of Version 2.0. (Learning Unit: 1221)
    Sub-tasks:
    1.1. Complete design of Search
    1.2. Complete design of Reporting
    1.3. Complete design of Visualization
    1.4. Merge all learning units from version 1.0 to Version 2.0
2. Apply survey and conduct analysis before Version 2 (Learning Unit: 1212)
3. Launch Version 2.0 Beta and conduct Usability test (Learning Unit: 1214)
4. Revise and launch Stable Version 2.0 (Learning Unit: 1215)
5. Apply survey and conduct analysis after Version 2 (Learning Unit: 1213)
6. Reason with learning units for knowledge discovery (Learning Unit: 1222)

13. Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

- Tasks are collections of research questions, problems, or hypothesis whose developments (contributions) may be described as learning units.

1221 We will complete the work in designing and implementing Version 2.0

1212 We will learn about the perception of CAMRA users about the use of the CAMRA KR Version 1.0 through a survey.

1214 A usability test will give us details on the quality of the user interfaces in Version 2.0

1215 We will launch Version 2.0. This will be an accomplishment unit.

1213 We will learn about the perception of CAMRA users about the use of the CAMRA KR Version 2.0 through a survey.

1222 This is the most intriguing scientific contribution of the year. We will reason with learning units using knowledge discovery algorithms. We are not sure yet what we will learn and/or how long it would take. We are more likely to produce units that will extend work in existing literature and we will refine hypotheses on what we will be able to discover. The work, in dose-response for example, has been intense and has an automated algorithm helping us make sense of this will be extremely interesting.

CAMRA OUTLINE FOR ANNUAL REPORTS

1. Integration-Projects (I-V): Applying and Transfer CAMRA knowledge

2. Investigators: Tomoyuki Shibata and Joan B. Rose Michigan State University and Yoshifumi Masago, Tohoku University

3. Project Goals (from proposal, additional goals):

- Applying CAMRA's knowledge to real world investigations,
- Transferring CAMRA knowledge to public by organizing workshops, and
- Assisting co-directors to manage CAMRA research activities as well as communications within and outside CAMRA.

4. Tasks* for Year (II):

- As part of Project I, we carried out experiments on microbial recoveries from different types of non-porous fomites using different methods (swabs and wipes) and attenuations based on cultivation method and qPCR .
- In Collaboration with Project II, we developed SOP for the influenza study and performed sample analyses.
- Based on dose-response models developed in Project III and risk management in Project, we created QMRA algorisms and frameworks
- For Project V, we organized QMRA workshops and the summer institute.

5. Research Activities

Completed units

- LU1048: Evaluating Swab and Wipe Methods for Viruses and Non-Spore Bacteria Recoveries from Nonporous Surfaces
- LU996: Organizing 1-day QMRA workshops at ASM 2007 General Meeting, Toronto Canada and International Water Association (IWA) Health Related Water Microbiology (HRWM) Symposium, Tokyo, Japan
- LU1038: Organizing 1-week QMRA Summer Institute 2007
- LU1050: Developing QMRA Instruction Manual 1st edition
- LU1257: Risk-based analysis of cryptosporidiosis outbreak at recreational water spray park in New York State

In progress units

- LU608: Gathering data on Cryptosporidium outbreak at Seneca Park, NY in Aug 2005
- LU609: Investigating P22 and *S. aureus* inactivation coefficients based on cultivation method and qPCR.
- LU619: Investigating the risk of pathogen exposures to children from sewage-contaminated beach sand risk assessment, pathogens, sewage spill, beach sand

- LU1125: Evaluating effectiveness of UV-HVAC system for improving indoor environmental quality in a hospital
- LU: Investigating potential long-term sources (water vs. soil) of outbreaks after flooding and interventions (chlorination, bottled water, and hand sanitizer) to reduce the infectious risk

6. Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

7. Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

- LU 1048.

Pre-moisten swabs, which are commonly used for fomite investigations, yield less recovery of P22 and *S. aureus* than pre-moisten wipes (Table 1). Based on the wipe method, the recoveries of P22 ranged from 10 to 78% (Table 2) and *S. aureus* ranged from 7 to 92% (Table 3) based on different fomite conditions. Although tested materials (aluminum, ceramic, glass, plastic, stainless steel, and laminated wood) and microbial concentrations (10^2 and 10^7 pfu/cm^2 for P22 and 10^3 and 10^6 cfu/cm^2 for *S. aureus*) could affect the recoveries, sampling area (10, 100, and 900 cm^2) was found to be the major factor. This study showed that the wipe method is the most useful for investigations of fomite-mediated diseases. We have also demonstrated that area of the fomite to be sampled should be taken into account when estimating the microbial concentration, as this can influence recovery rates (Figure 1 and 2)

.

Table 1: Comparisons of sampling tools and extraction reagents

P22	Fomite		% Recovery using swab			% Recovery using wipe		
(pfc/cm^2)	(cm^2)	Type	TSB	PBST	BF	TSB	PBST	BF
1.5 x10^2	10	CE	7.8 *(1.2)	7.8 (1.0)	15 (1.6)	69 (6.0)	70 (5.5)	69 (7.1)
1.5 x10^2	10	PL	3.0 (1.3)	22 (3.2)	13 (1.3)	61 (5.1)	79 (6.6)	28 (2.2)

* numbers in parenthesis are standard deviations

Table 2: P22 recovery and fomite conditions (concentrations, areas, and materials)

P22	Area	%Recovery from different types of fomites					
(pfu/cm^2)	(cm^2)	AL	CE	GL	PL	ST	WO
1.6 x10^7	10	60 (7.5)	53 (0.9)	59 (5.7)	65 (13)	67 (40)	68 (6.2)
1.3 x10^2	10	68 (6.0)	78 (4.3)	68 (7.2)	75 (8.4)	72 (1.8)	76 (5.8)
9.1 x10^1	100	50 (6.0)	54 (5.7)	55 (4.9)	49 (2.5)	46 (2.9)	41 (3.5)
1.2 x10^2	900	27 (6.0)	32 (3.9)	19 (8.6)	43 (23)	21 (3.3)	10 (4.0)

* numbers in parenthesis are standard deviations

Table 3: *S. aureus* recovery and fomite conditions (concentrations, areas, and materials)

S. aureus (cfu/cm^2)	Area (cm^2)	%Recovery from different types of fomites					
		AL	CE	GL	PL	ST	WO
3.9 x10^6	10	72 (9.7)	88 (11)	83 (13)	89 (14)	65 (37)	92 (6.8)
1.5 x10^3	10	87 (14)	88 (4.0)	78 (8.1)	71 (16)	73 (1.3)	68 (5.5)
2.1 x10^3	100	26 (2.9)	23 (3.0)	30 (0.6)	27 (1.5)	10 (3.0)	12 (4.8)
1.6 x10^3	900	11 (3.0)	8 (0.2)	17 (2.0)	13 (8.5)	7 (4.1)	8 (4.8)

* numbers in parenthesis are standard deviations

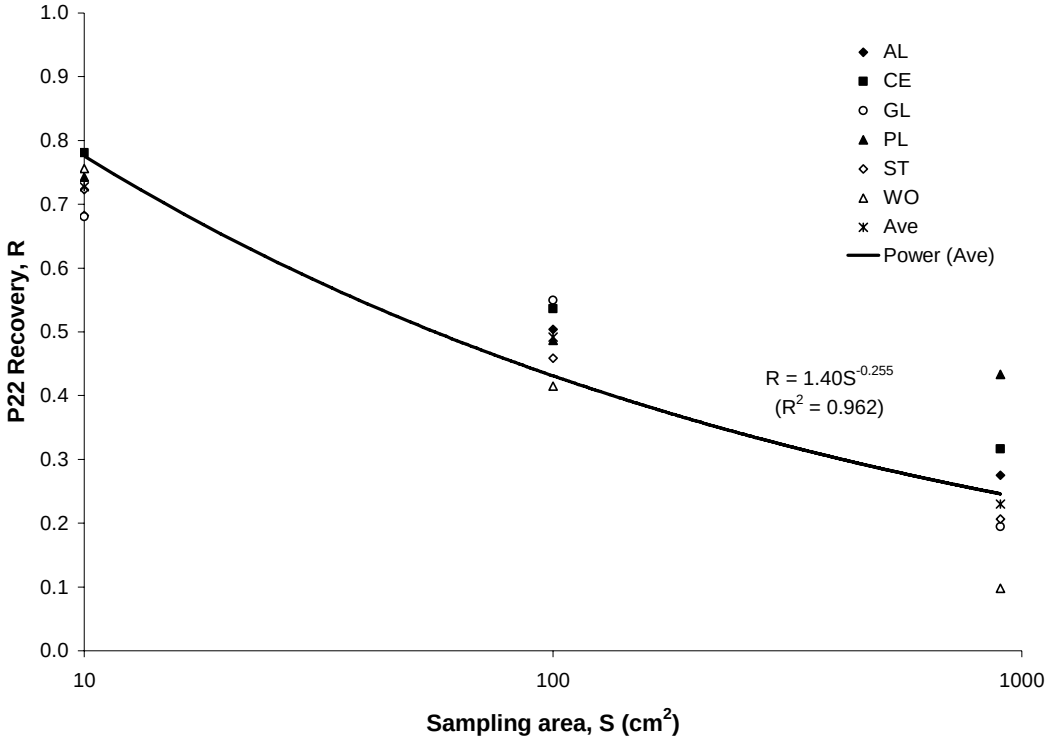

Figure 1: Relationship between P22 recovery, R and sampling area, S

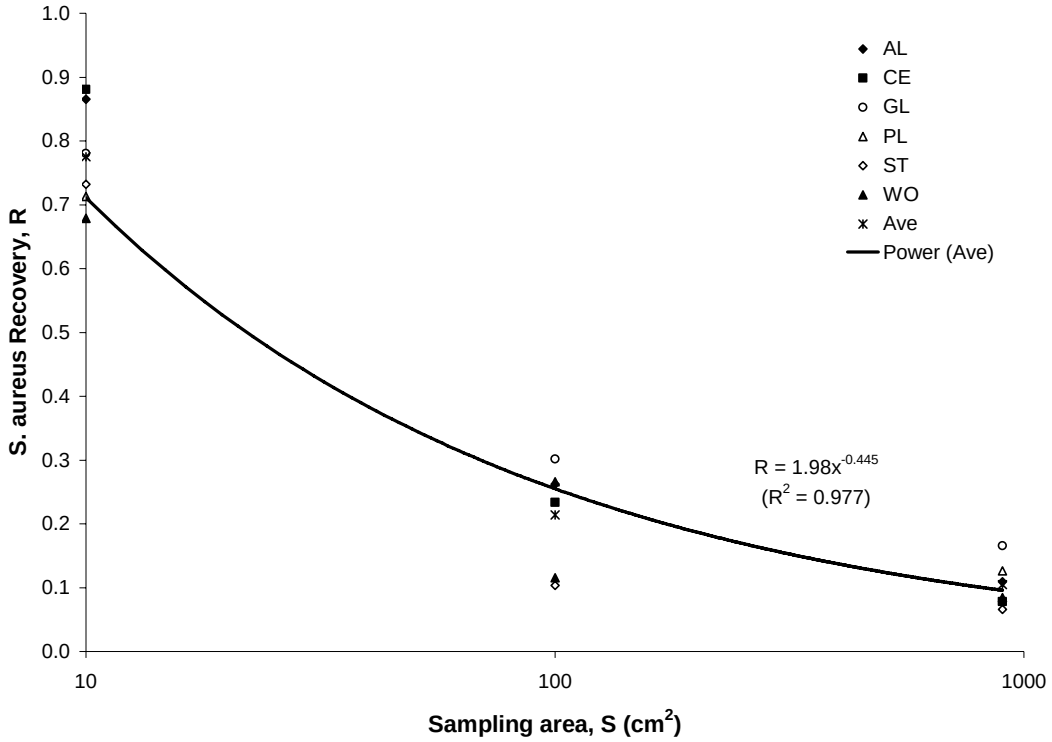

Figure 2: Relationship between *S. aureus* recovery, R and sampling area, S

- LU1257

A QMRA framework was developed to describe an outbreak of cryptosporidiosis in a spray ground in New York State. The developed model showed that a small amount of fecal release, such as accidental release from park visitors with cryptosporidiosis could raise the attack rate up to more than 10 %, which was enough to initiate the outbreak. Due to the insufficient water treatment system, *Cryptosporidium* concentration could remain very high for up to a couple of days. It was not possible to retain such a high risk for two weeks, unless as this analysis suggested that the outbreak was triggered and maintained by more than one patient visiting the park and releasing oocysts to the water circulation system.

The New York State has released new regulations (as a part of NYCRR Title 10, effective on March 28th, 2007) which require ultraviolet inactivation in addition to chlorination. The $\log_{10}$ inactivation rate of *Cryptosporidium* in water was 9 times higher than the previous treatment system. However, because only a part of drained water is to be treated by chlorination and UV inactivation before returning to the spray ground, it takes more than 6 hours to inactivate oocysts by 2 $\log_{10}$. It is recommended that the park should be closed for the entire day when fecal event is found.

Outputs:

8.1 Students Supported and/or Graduated:

- Tomoyuki Shibata, postdoctoral fellow
- Yoshifumi Masago, visiting research fellow (funded by Japan Society for the Promotion of Science)

- Leilei Qian, Ph.D. student (since August 2007)

8.2 Publications:

- Six proceedings have been published for national and international conferences (see presentations).
- Several manuscripts are in progress now.

8.3 Patents: None

8.4 Presentations:

- Masago, Y. and Rose, JB. Risk-based analysis of cryptosporidiosis outbreak at recreational water spray park in New York State. International Water Association (IWA) Health Related Water Microbiology (HRWM) Symposium, Tokyo, Japan, September 9-15, 2007.
- Shibata, T. and Rose JB. 2007. Quantitative microbial risk assessment of water-related disasters (Poster). International Water Association (IWA) Health Related Water Microbiology (HRWM) Symposium, Tokyo, Japan, September 9-15, 2007.
- Shibata, T. Advances in microbial risks toward enhancing water supply securityater security. American Water Works Association (AWWA) Michigan Water Security Summit, Lansing, MI, June 6, 2007.
- Herzog, AB., Pandey, A., Shibata, T., Rose, JB., and Hashsham, SA. Implications of detection limit of various methods of Bacillus anthracis in computing risk to human health (Poster). 107th General Meeting of the American Society for Microbiology (ASM), Toronto, Canada, May 21-25, 2007.
- Masago, Y., E.K. Lipp, J.C. Futch, D.W. Griffin and J.B. Rose. Human recreational risk in nearshore waters of the Florida Keys (poster). 107th General Meeting of the American Society for Microbiology (ASM), Toronto, Canada, May 21-25, 2007.
- Shibata, T., Cologgi, DL, Masago, Y., Shumate, WJ., Williams, LB., Dials, K., and Rose, JB. Evaluation of virus recovery methods from fomites using a Virus surrogate, bacteriophage P22 (Poster). 107th General Meeting of the American Society for Microbiology (ASM), Toronto, Canada, May 21-25, 2007.

8.5 Participation or organization of workshops:

- 1-Day QMRA workshop, International Water Association (IWA) Health Related Water Microbiology (HRWM) Symposium, Tokyo, Japan, September 9, 2007.
    - Masago organized the workshop and lectured “Risk Characterization and management”
    - Shibata instructed QMRA exercises
- 2nd QMRA Summer Institute, Michigan State University, East Lansing, MI, August 19 - 23, 2007.
    - Shibata organized the summer institute and lectured “Exposure Assessment”

- 1-Day QMRA workshop, American Society for Microbiology (ASM) General Meeting, Toronto, Canada, May 20, 2007
    - Shibata organized the workshop and lectured "Exposure assessment"
    - Masago organized the workshop and instructed QMRA exercises

8.6 Case studies, algorithms developed:

- Cryptosporidiosis outbreak at recreational water spray park in New York State.
- Flooding in a developing country and intervention to reduce infectious risk

8.7 Human Resource Development: None

8.9 Other (consulting, interviews, etc.): None

8.10 Funds Leveraged (additional funding, resources for free): None

9. Outcomes (how your contributions can be used to better society):

- Validated wipe method is useful for other researchers and federal governments to perform further quantitative investigations of fomite contaminations in order to understand the role of fomites in the spread of pathogens such as influenza, norovirus, and MRSA, or potential biological threats, and to develop a standardized method for consistent and comparable results
- Organized two 1-day workshops and summer institute contribute spreading QMRA along with CAMRA's updated knowledge to government employees, researchers and graduate at universities and industries.
- Small fecal release from patients carrying infectious agents in spray ground can cause large outbreaks. The developed QMRA framework is useful in developing water management guidelines in spray parks.

10. Collaboration with other Projects (actual work in collaboration within and outside CAMRA):

- with Syed Hashsham (Project I): Advising fomite sampling method
- with Joseph Eisenberg and James Koopman (Project II): Developing SOP and analyzing samples for Influenza study
- with Charles Haas (Project III) and Mark Nicas (Project I): Developing QMRA framework for TB in the airplane
- with Rosina Weber (Project V): Assisting improvement of the KR system

11. Integration with other projects (association between units in different projects):

- Fomite sampling method (Pre-moisten antistatic wipe with PBST-80 extraction) in LU1048 (Evaluating Swab and Wipe Methods for Viruses and Non-Spore Bacteria Recoveries from Nonporous Surfaces) is used by following units
    - LU1086: Environmental agent assessment during influenza season of winter 2007 in the university residential halls setting

- LU 844: Detection limit of qPCR and Cultivatable Methods using P22 Herzog, Amanda
- LU 1165: The Evaluation of Detection Limit for qPCR and Plaque Assay Using Bacillus thuringiensis and P22 from Large Surface Areas
- LU 1125: Effectiveness of UV-HVAC system for improving indoor environmental quality in a hospital

12. Tasks for Next Year (see definition below):

- Complete an investigation on P22 and S. aureus inactivation using cultivation method and qPCR
- Complete QMRA on pathogen exposures to children from sewage-contaminated beach sand risk assessment, pathogens, sewage spill, beach sand
- Complete QMRA on outbreak associated with flooding and intervention
- Complete evaluation of effectiveness of UV-HVAC system for improving indoor environmental quality in a hospital
- Revise QMRA Instruction manual
- Organize 1-day QMRA workshop at American Society for Microbiology, 2008
- Organize 3rd QMRA Summer Institute in August 2008

13. Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

It is anticipated that risk management plans based on QMRA will be developed to reduce potential outbreaks associated with 1) spray park, 2) sewage spill on the beach, and 3) flooding in developing countries. The wipe method would bring novel findings associated with fomite mediated transmission diseases.

* **Tasks** are collections of research questions, problems, or hypothesis whose developments (contributions) may be described as learning units

EXPENDTURES

Table: CAMRA Expenditures from September 2005 to August 31 2007

University	Given to Univ, Year 2	Given to Univ, Cumulative	Project	PI	Given to PI, Year 2	Given to PI, Cumulative	Expenditures Year 2	Expenditures, Cumulative	% of YR 2 Budget	Total Expenditure %
Michigan State University	$ 481,441.00	$ 904,220.00	Co-Director	Dr. Rose	$ 300,332.00	$ 547,614.00	$ 196,581.94	$ 260,875.94	80%	53%
			I	Dr. Hashsham	$ 181,109.00	$ 356,606.00	$ 112,626.33	$ 144,041.36	62%	40%
			III	Dr. Bolin	$ -					
			V	Dr. Todd	$ -					
University of Arizona	$ 193,351.00	$ 396,605.00	I	Dr. Gerba	$ 95,837.00	$ 196,582.00	$ 101,763.62	$ 176,319.62	106%	90%
			I	Dr. Choi	$ 97,514.00	$ 200,023.00	$ 89,554.22	$ 169,681.00	92%	85%
Northern Arizona University	$ 103,816.00	$ 205,255.00	I	Dr. Keim	$ 103,816.00	$ 205,255.00	$ 70,597.64	$ 84,144.64	68%	41%
University of California, Berkeley	$ 162,134.00	$ 319,747.00	I	Dr. Nicas	$ 162,134.00	$ 319,747.00	$ 135,013.62	$ 190,261.48	83%	60%
University of Michigan	$ 229,743.00	$ 529,196.00	II	Drs. Eisenberg	$ 229,743.00	$ 529,196.00	$ 193,579.00	$ 366,289.00	84%	69%
Drexel University	$ 458,226.00	$ 912,555.00	Co-Director	Dr. Haas	$ 111,743.00	$ 218,303.00	$ 89,494.62	$ 115,572.07	80%	53%
			III	Dr. Haas	$ 146,483.00	$ 254,249.00	$ 53,262.99	$ 83,555.49	36%	33%
			IV	Dr. Gurian	$ 80,000.00	$ 170,003.00	$ 29,259.06	$ 52,932.13	37%	31%
			V	Dr. Weber	$ 120,000.00	$ 270,000.00	$ 75,994.82	$ 173,429.62	63%	64%
Carnegie Mellon University	$ 94,632.00	$ 194,401.00	IV	Dr. Casman	$ 94,632.00	$ 194,401.00	$ 35,656.00	$ 11,739.00	38%	6%
Total	$ 1,723,343.00	$ 3,461,979.00			$ 1,723,343.00	$ 3,461,979.00	$ 1,183,383.86	$ 1,828,841.35		

Note: Official contracts were completed between April and June 2006 and work by PIs began after the first All PI meeting in 2006 although CMRA was established September in 2005