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June 26, 2008

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Dr. Lawrence Reiter
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Dear Drs. Gray and Reiter:

This letter report from the Board of Scientific Counselors (BOSC) provides specific advice and guidance to the National Exposure Research Laboratory (NERL) on the development and implication of the Laboratory's Conceptual Exposure Framework document. The BOSC NERL Standing Subcommittee (NERLSS) was briefed by the NERL Laboratory Director and Associate and Division Directors over the course of a 2-hour teleconference and a 1.5-day face-to-face meeting in Research Triangle Park, North Carolina, on December 11-12, 2007. The NERLSS members include Kenneth Demerjian (Chair), Steve Bartell, Joseph DePinto, Douglas Dockery, and Michelle Frey. The members' affiliations are presented in Appendix A.

This was the first formal convening of the BOSC NERLSS, whose purpose is to provide advice and guidance through periodic interactions with NERL management and staff on a variety of programmatic and operational issues facing the Laboratory. The first meeting entailed briefings to introduce the organization and mission of the U.S. Environmental Protection Agency's (EPA's) Office of Research and Development (ORD) and NERL, followed by an overview of the principal science capabilities within NERL. The background introductory materials led into the primary focus of the meeting, which was to be briefed on the NERL Exposure Framework document. The NERLSS was asked to provide commentary on this document as framed

within a series of charge questions presented to the Subcommittee prior to the face-to-face meeting. The charge is provided in Appendix B.

The detailed response to the charge questions by the NERLSS that follows summarizes the Subcommittee's advice and guidance regarding the Exposure Framework document and the feedback provided during the face-to-face meeting. Overall, there is unanimous agreement among Subcommittee members that the effort and time commitment of NERL management and staff to prepare the Exposure Framework was time well spent and that the document, which is expected to evolve with time, does provide a unifying theme and cohesiveness that will bring the six divisions into closer working relationships. Principal recommendations drawn from the Subcommittee members' detailed comments are as follows:

- ✍ The communication of the vision of the Exposure Framework to the other ORD laboratories and centers to develop a sense of ownership ORD-wide is important and dictates that the document be vetted by the other laboratories and centers before it is finalized.
- ✍ Consider separating the Framework into two core documents—one document addressing the NERL/EPA Guidelines to Exposure Science and Research, and the second document describing internal management practices at NERL in implementing the Framework.
- ✍ The first document should be viewed as an EPA guidance document, founded on best practices and principles for sound exposure research and estimation techniques. This guidance document should be followed up with a peer reviewed journal article describing the scientific basis of the Exposure Framework. This document should include a detailed description of its target audience. Indeed, there are multiple audiences which will require somewhat alternative documents. In addition, the document should identify and work through one human health example and one ecology example to truly assess its utility and clearly identify the process and prioritization criteria applied in setting the research agenda.
- ✍ The second document describes the implementation framework, focusing on NERL practices in terms of: (1) mission and goals, (2) management strategy, (3) research and financial planning process, and (4) administrative procedures. Although it is not in the interest of NERL to write a “management book,” it is important to NERL operations and for staff to have an internally focused “rule book” of how the laboratory will pragmatically carry out its mandate.
- ✍ The Framework document has great value in defining the field of “exposure science” for the broader scientific community. In that context, it is important that the document clearly state its goals and audiences in the introduction and be written in such a way that it is sensitive to the broader role it will be playing. This means being very careful and inclusive in how the document defines and explains exposure science and research in Sections 2 and 3 of the document.

- ✍ The illustration of the source-to-outcome continuum holds for human health and ecological exposures, Figures 2-3 and 2-4, respectively. NERL should consider using a single diagram with text highlighting the complexities of media interactions and the differences in the demands of the research disciplines (as outlined in the text box on page 5 of the Framework document).
- ✍ The Framework document needs to further clarify how program areas for which the responsibilities are divided among ORD laboratories (e.g., water quality research) will be addressed under the proposed construct.
- ✍ The Framework should be applied as part of the research planning process, with a follow-up post-audit to assess the effectiveness of the document and help highlight the areas of the framework that need to be strengthened.
- ✍ The Framework document needs to better articulate NERL's partnering goals and agenda.

Response to Charge Questions

1. Effectiveness of the NERL Exposure Framework

The NERLSS believes that the Framework (<http://www.epa.gov/nerl/recentadditions.html>) has provided a unique opportunity for NERL to identify itself as a cohesive organization under a common mission. Overall, the Exposure Framework identifies the principal elements of exposure science and can serve as a guidance document for both internal and external use by the Agency. One of the fundamental goals of the Exposure Framework is to draw together and focus the diverse disciplinary research programs underway within the six divisions reorganized under NERL, thereby identifying the common core science threads associated with exposure assessment across media. Based on presentations and discussions with Division Directors at the face-to-face meeting, the Framework seems to have accomplished this goal at the management level. The blue print has been accepted; what remains to be demonstrated is the divisions' ability to support and implement the principal elements of the Framework and meet other obligations/demands of their clients.

(a) Please comment on the effectiveness of the Framework in describing the elements of exposure science.

The introduction of the Exposure Framework document states the genesis of the document and the objective of each of the subsequent sections. It would be valuable, however, to include in the introduction (probably in the paragraph just prior to the stated section objectives) a statement of the primary and secondary audiences for the document. Based on discussions during the meeting, it seems clear that the primary audience is the NERL research community itself. There is a desire for everyone within NERL to gain the same understanding of "exposure science and research" and to understand how the laboratory will identify and prioritize its exposure research program. The document also has potentially great value in defining the field of "exposure science" for both EPA and the broader scientific community and provides the opportunity for NERL to take a

leadership role in defining exposure science. Accepting this responsibility requires careful consideration in the preparation of Sections 2 and 3 of the Framework document. With that in mind, there are a variety of comments from NERLSS members regarding Figures 2-1 through 2-4 and 3-1, which do not necessarily form a consensus of opinion as to how those figures should be revised but do point out the diverse perspectives of the disciplines represented. Specific comments regarding these figures are presented in the following paragraphs.

Figures 2-1 through 2-4 and 3-1 and the corresponding text provide a useful description of the elements of exposure science for the purposes of the Framework. The document strikes a reasonable balance between completeness and detail without attempting to serve as a textbook for exposure science.

Figures 2-3 and 2-4 should be revised to emphasize similarities and differences in exposure research for humans and other organisms. For example, in Figure 2-3, the box that includes individual, population, community, and ecosystem needs to be removed or modified to identify individuals and sensitive subpopulations, and that same box (i.e., individual, population, community, and ecosystem) in Figure 2-4 should be moved up to the effects box. The point is that ecological effects are of interest at additional levels of biological/ecological organization compared to human health effects. Exposure regarding populations and communities still is fundamentally the collective exposure of individual organisms that constitute these higher levels of organization. Exposure at larger spatial (and temporal) scales is not the same as “ecosystem” exposure, even for physical and biological stressors. One NERLSS member suggested removing ecosystem exposure from the lexicon as well as the cascade of effects arrows from all of the boxes, except perhaps the source/stressor box. A point made in the face-to-face discussions was that an affected ecological “entity” might serve as an additional stressor. (The same case can be made for infected humans.) The arrows to the other boxes may not be necessary, may be confusing, and may be both. Also, ingestion of contaminated food is a central issue in characterizing exposure for organisms, so “food” should be added to the box beneath ambient concentration.

The sequence of steps involved in characterizing exposure is not a “continuum” at all and nothing is gained by using this terminology. It may be useful to note that these steps might not require sequential execution. For example, an ambient concentration might be simply measured and support an exposure assessment without the need to understand the complex chemistry, fate and transport, and so forth. This additional information might be used in subsequent mitigation planning, but it is not essential for risk characterization. Also, “ambient concentration” is probably not inclusive terminology to address physical and biological stressors for ecological exposure research (i.e., Figure 2-4).

One possible solution regarding Figures 2-3 and 2-4 is to have only one figure accompanied by commentary pointing out that the system is far more complex than depicted as a result of feedbacks and interactions across various media; the text box on page 5 identifies some of the main differences between the human health and ecological research disciplines.

Figure 3-1 has been generally referenced as a seminal depiction of the flow of exposure science information and therefore the basis of NERL's mission. Using a more fleshed-out example, NERL should examine how well Figure 3-1 can be applied in terms of distinguishing between exposure assessment work and exposure science research. This exercise may simply be useful in validating the content and direction of the Framework document. See Appendix C for a specific example of such an exercise.

The Exposure Framework provides a very simplified version of the elements of exposure science and does not address more complex exposure science requirements. For example, multimedia and multipathway exposures often are treated as exchangeable concepts. The media of an exposure (food, water, air, soil, drugs, personal care products, etc.) is the environment in which the stressor exists as it either interacts with the receptor directly or indirectly. The pathway is the specific mechanism of stressor introduction to the receptor (e.g., for humans it is ingestion, inhalation, dermal). These two concepts need to be kept separate and yet in today's exposure science world, must both be addressed in research program development as appropriate.

When multiple media forms can introduce a stressor to receptors using the same pathway, then the relative source contribution determination is necessary and should be integrated into NERL's conceptual model of exposure research. Further, if the total body burden of a receptor to a stressor is important and multiple pathways can contribute to that burden, then the exposure science research must find ways to address both cross-media and multi-pathway stressor dosimetry. This also raises the question as to whether or not dosimetry is within the domain of exposure research or the domain of health effects research. Dosimetry appears as a likely grey area that should be mentioned in discussing the source-to-outcome continuum.

(b) There are both similarities and differences in exposure science as it is applied to humans and ecosystems. Within the document, the authors tried to use concepts and terminology that could be applied to both disciplines with a discussion of differences only where necessary. Does the document provide a meaningful discussion for both disciplines? Are there recommendations for bridging the understanding of exposure research for both groups?

One of the challenges of this Framework, and indeed one of the challenges in managing NERL, is bridging across the divisions of NERL that traditionally have focused either on human health or ecology.

The Framework as presented follows paradigms that are well known in human health research, and specifically in air pollution studies. The application of the principles of human health exposure science to ecological studies represents a clear challenge. That the ecologists have been able to describe the steps in ecological exposure assessment in this human health Framework is a substantial achievement in itself and speaks to the willingness of NERL scientists and managers to work together constructively. Nevertheless, the attempt to fit ecology, or even water quality, to this paradigm at times seems forced and unnatural. This is not to undervalue the benefits of having all of the NERL divisions participate in constructing this Framework and in identifying these unifying principles.

The Framework is, at this point, a conceptual model. Its utility will be demonstrated through application. Thus, the NERLSS recommends that specific examples in air pollution, water quality, and ecology be developed and presented as part of the extended Framework.

The human health exposure assessment path is very linear and perhaps over-simplified. Some general questions about how NERL perceives human health issues include:

- (1) Cascade effects critical to both the Homeland Security and Drinking Water Research Programs are secondary infection spread in terms of likely exposure predictions and “event” consequences. Is this within NERL’s domain for human exposure?
- (2) How does biotransformation from a negligible impact to a severe impact stressor get integrated into the Exposure Framework and discussion for human health? Whereas inhalation exposure has filtration and transfer from lungs to blood, ingestion introduces chemical changes in constituents (especially metals) in the stomach and gastrointestinal (GI) tract. This typically is considered part of the dosimetry process within exposure assessment. Is this part of NERL’s domain, and if so, do these biotransformations create a “cascade of effects” (positive or negative) within the receptor?
- (3) How are autoimmune system impacts, birth defects, and severe cognitive impacts considered in terms of cascade effects? The ecology exposure assessment references bioaccumulation impacts and the complexities inherent in them due to this factor. The discussion in the Framework, however, seems to ignore human health effects commonly attributed to bioaccumulation exposures (e.g., mercury in fish).

Although the generalities may hold in describing a more simplified human risk assessment pathway, this simplified view must be set aside for a more accurate and profound perspective on human health.

Also, how is ecological exposure related to human exposure by the Framework? There is no evidence mentioned in the Framework that identifies this relationship.

(c) Please comment on the effectiveness of the Framework in describing the uses of exposure science in furthering the Agency’s mission to protect human health and the environment.

One of the strengths of the Framework is the specification of the utility of exposure science to the Agency. In large part, this utility is defined in terms of EPA’s responsibility to manage risk and minimize exposures to environmental stressors. The value of exposure sciences for health effects research, however, is not explicitly mentioned. Environmental epidemiology depends importantly on quality exposure assessment. Epidemiology might not unequivocally demonstrate causal relationships, but epidemiology has provided statistical descriptions of adverse health effects measured in populations exposed to environmental stressors. Epidemiology can provide insightful exposure and health response outcomes.

The Framework, in many places, refers to the need to be client- or customer-oriented; however, the client or customer is never explicitly defined. Implicitly, the most important client appears to be the Agency, and specifically the groups within NERL. Nevertheless, the National Health and Environmental Effects Research Laboratory (NHEERL) also would be a user of these exposure data. Indeed, these data also could be a major resource for extramural investigators. Thus, in defining NERL's clients, consider the research as well as the policy arms of EPA, and, secondarily, extramural as well as intramural users.

Section 3 of the Framework outlines NERL's contribution to supporting EPA's mission mainly through reference to enabling legislation and the identification of four primary areas, including: development of current standards/policies, achieving same, evaluation of impacts of same, and development of science for the next generation of standards/policies. Additional discussion focuses on mitigation (i.e., Is mitigation necessary? How to best mitigate? Was the mitigation successful?). The Framework rightly recognizes the usefulness of this approach in addressing historical Agency needs in the context of standard-based mitigation for single stressors, sources, and pathways. The Framework correctly takes the next step by outlining how this paradigm will need to be modified to address more realistic exposure scenarios of multiple stressors, sources, and pathways. Importantly, the NERL Framework for research planning provides a management vehicle for developing the necessary exposure science to support these real-world exposure scenarios.

The Framework document does not include any clear articulation of the decision-making process for prioritizing competitive research needs. Given resource and time limitations, NERL certainly will face the question of how its limited resources are to be distributed to gain the greatest value for its expenditures. To this end, a prioritization procedure should be integrated into the Framework. Based on the content provided by NERL, Appendix D (Exhibit 2) illustrates an example of such a prioritization procedure.

2. What are the core areas of expertise that are required within NERL to effectively conduct human health and ecological exposure research? How are these areas likely to evolve in the future?

Given the historical and continuing technical contributions of NERL to human and ecological exposure science, the Laboratory clearly possesses the necessary core areas of expertise. The following technical capabilities will undoubtedly remain important in future NERL exposure research: environmental sampling in various media, sample preservation and processing, development and application of state-of-the-art methods in analytical chemistry, data management and reporting systems, environmental chemistry, environmental fate and transport modeling, statistical analysis, quality assurance/quality control (QA/QC), and documentation of exposure profiles. NERL's development of the Community Multiscale Air Quality (CMAQ) modeling system and ongoing research on downscale coupling and improved subgrid-scale treatments of local sources will improve exposure estimates and will evolve and benefit the exposure assessment community in the future.

The Framework defines exposure model development as a major function of NERL. Exposure models must be evaluated within the context of measured exposures. Model validation is crucial. NERL is well positioned in traditional methods and expertise relevant to exposure assessment. The cutting-edge science in exposure assessment, however, is based on biologic measures of exposures. Highly sensitive methods for measuring environmental contaminants in biological samples are being routinely used for surveillance of U.S. population exposures by the Centers for Disease Control and Prevention (CDC). The Subcommittee encourages NERL to use biologic monitoring to evaluate the performance of Agency exposure models.

Previous exposure research at NERL has focused on potentially toxic chemicals, often in relation to fairly localized contamination. In addition to chemicals, however, future Agency requirements increasingly will emphasize physical (e.g., habitat degradation/loss, climate change) and biological (e.g., invasive species) stressors. New chemicals of potential concern (e.g., cosmetics, antibiotics, common household products) will receive increasing attention as technical capabilities in analytical chemistry increase. These relatively new topic areas in exposure science will require the expansion of current chemical exposure capabilities and the development of new technologies to characterize wide-scale distribution of minute concentrations of a large number of potentially important compounds. Commensurate with the new analytical needs are advances in the ability to characterize complex exposure profiles for novel chemicals, including the possibility for increased interactions among chemicals (e.g., synergy, antagonism, additive) that might influence exposures for humans and other organisms. Continued advances in genomics and environmental proteomics might supply the necessary sophistication to determine exposures to novel chemicals, either individual chemicals or mixtures.

It will become increasingly important to obtain fine-scale temporal observations over large spatial scales (e.g., synoptic measures of climate change). Abilities to characterize population exposure, habitat quality, and distribution in relation to stressors affecting landscapes will require continued expansion of capabilities in satellite imaging, remote sensing, monitoring, and landscape ecology. Attendant to new challenges in remote data collection are needs for analysis and presentation of these data and results of analyses. Compatible modeling approaches must be advanced to interface with large-scale and potentially “real-time” monitoring efforts. Models that emphasize forecasting, including explicit consideration and propagation of uncertainties, will be needed. Parallel monitoring and modeling capabilities are needed for characterizing the invasion, spread, and establishment of exotic species in terrestrial and aquatic environments.

Nanotechnologies will increasingly become the subject of exposure and risk assessment. Innovative tools for identifying, sampling, and describing the distribution and abundance of potential “nano-stressors” in relevant media will be needed. Conceptual advances are needed in describing what “exposure” means within the context of nanotechnology human and ecological risks.

Ingestion pathway exposure research is not identified among NERL’s core competencies and responsibilities. If NERL is to fulfill the mission described in the Framework, then it should be the authoritative group on exposure science and its application in support of EPA programs, including drinking water (Safe Drinking Water Act [SDWA]) and recreational water (Beaches

Environmental Assessment and Coastal Health Act), and in performing relative source contributions for various ingestion exposures (e.g., food, drinking water, environmental water). In fact, the differences in the state-of-the-science in air exposure modeling and drinking water exposure modeling clearly demonstrate the immaturity in ingestion exposure science at this time. NERL's current organizational structure may not be well suited to encompass this task or expertise, but strategies should be implemented to bring NERL knowledge, practices, and experience to ingestion pathway exposure research. This may be an area in which NERL has not taken a leadership role and needs to step forward now to assure that the same principles of good science are used Agency-wide in performing exposure research.

3. How can we use the Exposure Framework as a communication tool?

NERL should consider separating the Framework into two core documents. One document should be the *NERL/EPA Guidelines to Exposure Science and Research*. This should be founded on the best practices and principles for sound exposure research and estimation techniques. The Guidelines would encompass the first three chapters of the current Framework document, expanded appropriately and perhaps with contributions from other EPA and non-EPA groups.

The second document should be the Framework, which would be focused on describing the practices of NERL in terms of its: (1) mission and goals, (2) management strategy, (3) research and financial planning process, and (4) administrative procedures. Although it is *not* in the interest of NERL to write a "NERL management handbook," it is important to NERL operations and staff to have an internally focused document that describes how NERL will pragmatically carry out its mandate. This is critical to keep NERL staff engaged and focused on NERL products and services. It also is vital to sustaining an organization through shrinkage and expansion periods, succession processes, and continually evolving scientific challenges.

(a) To enhance external communications?

As a communication tool, the Guidelines document would provide the greatest advantage of aligning public and scientific thought about exposure science and its practice in environmental policy. This is a critical requirement for the effective use of funds, skilled resources, and scientific endeavor among the various ORD organizations. Further, exposure science will continue to evolve, and the Guidelines as well as NERL's specific program requirements also will have to remain dynamic. In fact, the evolution should in large measure be driven by a commitment to continuous improvement and exploration by NERL researchers and administrators. Remaining relevant to the national environmental policy debate is critical for NERL's continued success and proper utilization.

In reality, the external communications of NERL will be enhanced with the creation of these two documents. The process undertaken to create them will enable NERL staff and management to better articulate NERL's mission, capabilities, needs, and role in ORD and EPA, and to become more productive ambassadors. There are, however, additional materials that could be developed to assist with outreach both within and outside of EPA. These materials might include, for example, (1) an Exposure Science Guidelines publication, (2) an abstract/summary of the

Guidelines, (3) a standard presentation about the Guidelines, and (4) frequently asked questions (FAQs) about NERL and the Guidelines.

The internal adoption of the Framework should include a formal outreach program for NERL administrators, research scientists, and staff. The program should include such materials as: (1) a standard presentation on the Framework for Division Directors and Assistant Directors to provide to staff, (2) a Research Planning Process Fact Sheet that summarizes the procedures that NERL will adopt in its research planning process, and (3) a “How-to Guide” for scientists to participate in the research planning function.

Perhaps the most important internal use of the Framework is to guide the planning and funding of NERL research. NERL success depends on the scientific excellence of its researchers. Maintaining a culture of value for scientific excellence is therefore vital, and in doing so, NERL scientists and administrators must determine the direction of their research and define the resulting products, while balancing the productive use of staff time and resources in implementing the research and financial planning process.

Several steps can help NERL to improve its future research planning and prioritization process, and these steps should be evaluated for their suitability by NERL (see Appendix D, Exhibit 2). Consideration of improvements, however, should not delay the publication of the current Framework for internal uses.

(b) To develop new partnerships?

External communications should be focused on the Guidelines and not on the Framework. Clearly, as the Implementation Plans (IPs) are developed and research opportunities to collaborate with other organizations are identified, communication regarding those specific requirements will be necessary; however, this is not really a use of the Framework for external outreach or education.

NERL has experience in communicating its mission and capabilities to partners within and external to the Agency but should better articulate its partnering goals and agenda in the Framework document and use it to enhance the community dialogue on the Agency’s mission.

The Framework is based on the human health/air pollution model. Although the fine particulate matter (PM_{2.5}) example is presented to demonstrate the utility of the Exposure Framework, the information presented does not clearly show the advantage of the Framework. The Subcommittee encourages NERL to include other human health and ecological examples.

The NERLSS believes that presentations on the framework and its use throughout NERL at the division level would stimulate interest and lead to substantive comments and revisions that could further improve the document. Following this iteration, the Framework should be presented to the rest of ORD, to the EPA program offices, and to the scientific community outside of EPA through publications (both peer-reviewed and commentary/white paper type) and at appropriate scientific conferences.

4. Please comment on the merits and barriers to conducting the exposure-related collaborative, multidisciplinary research that will be required to successfully address the full suite of risk assessment and risk management activities.

The principal merit of the collaborative, multidisciplinary research encouraged by the Framework is that this type of research addresses the complex, multidisciplinary risk assessment problems that now largely drive NERL. The increasing importance and necessity of considering multiple stressors, multiple pathways, and multiple media in the evaluation of cumulative risk (both human health and ecological) requires the implementation of the new research model outlined in the Framework. Collaborative, multidisciplinary research is needed for NERL to contribute effectively to the Agency mission.

An additional benefit for collaborative, multidisciplinary research lies in the opportunity for new and important scientific discovery. For example, the integration of atmospheric and ocean circulation studies made possible the discovery of the Northern-Southern Oscillation (El Niño), whereas such a key phenomenon remained undiscovered in previous investigations by atmospheric scientists and oceanographers working independently. As EPA needs increasingly emphasize physical (e.g., climate change) and biological (e.g., invasive species) stressors, the NERL Framework can provide the impetus and opportunity for important scientific breakthroughs in terms of understanding complex physical, chemical, and biological interactions that underlie not-yet-described phenomena that might importantly determine human and ecological risks. Of course, multidisciplinary (e.g., environmental sampling, analytical chemistry, and fate and transport modeling) efforts remain important in describing and quantifying individual physical, chemical, and biological processes that are fundamental to advancing basic and applied exposure science. Such opportunity for key scientific discovery and continued advances in exposure science (i.e., core research) should be stressed in the presentation of the Framework to each NERL division.

The NERL Framework rightly identifies several barriers that must be surmounted for successful implementation. Planning research across several management levels can potentially result in a complex set of research plans that reflect different (diverse) planning efforts and require participation by different team leaders and participating staff. Corresponding plans and organization might become overly burdensome. Perhaps the best solution to this potential problem lies in simply “working the plan” and using the resulting experience to revise, streamline, and adapt the planning process as necessary. Discussions during the face-to-face meeting suggested that Division Directors and NERL headquarters staff intend to be flexible in implementing the overall planning process. The accumulated NERL experience of working through the research planning process across management levels will undoubtedly identify those elements of the Framework that are conducive to planning successful collaborative and multidisciplinary research efforts. Bottlenecks and sources of conflict in these planning efforts will be correspondingly pinpointed and can be subsequently addressed by adapting the NERL Framework and planning process.

Collaborative team research, especially across organizational and geographical boundaries, poses challenges in terms of development, management, resource allocations, rewards, and evaluation. This research model, which departs significantly from the more traditional individual principal investigator (PI) model, requires the willing and unselfish participation of increasingly fewer available research staff. To be successful in addressing these challenges, the implementation of the Framework must be entirely transparent to those individuals most affected. The opportunities and rewards for participation must be individually understood, and the value of productive team research must be recognized and rewarded at the division and higher levels of management within NERL. Additional rewards or motivation for collaborative participation might take the form of preferential allocation of technical support staff, new equipment purchases, or availability of other valued research infrastructure (e.g., laboratory space, experimental facilities) within NERL.

Discussions concerning the importance of collaboration as part of the review process for promotion within NERL indicate that management subscribes to the new research model. The desired participation of NERL technical staff in the design of the Multi-Year Plans (MYPs) and IPs as outlined in the Framework demonstrates some necessary transparency in the overall planning process. At the same time, the Framework importantly recognizes that all NERL research need not be multidisciplinary; the traditional research model remains valid and valuable, particularly for those individual PIs whose work brings substantial extramural funds into NERL. Additional trust in the planning process might result from encouraging PIs to participate, even sparingly, in multidisciplinary projects in addition to maintaining their strong individual research programs, and opportunities and rewards for collaborative and multidisciplinary research within NERL should be clearly addressed in the presentations of the Framework made by each Division Director.

Challenges posed by the need for collaborative, multidisciplinary research also might be effectively addressed during the hiring process within NERL. Special consideration could be given to those candidates who have participated in multidisciplinary research projects, value the collaborative research model, and are more broadly trained—or at least broadly interested in exposure research.

The foundation of strong epidemiologic research is good exposure assessment. There are many opportunities for improving existing epidemiologic studies and for creative use of NERL exposure resources in designing new epidemiologic studies. For example, the well-developed NERL models for forecasting ambient air pollution concentrations would be highly valuable as a resource for back-casting ambient air pollution for epidemiologic health effects studies. In addition, layering modeled estimates, ambient network data, and remote sensing (satellite) data could be very informative in estimating exposures spatially in data-sparse areas and temporally in regions with intermittent monitoring. Consider including epidemiologists, both intramural and extramural, as customers (or clients) of the NERL exposure assessment tools and methods.

The document should be used in the research planning process and in making decisions about new staff recruitment or re-direction of existing staff research, and NERL should develop a formal and structured process to evaluate its success in promoting effective collaborative, multidisciplinary research on exposure problems that serves both the problem-based and core-based aspects of its research mission.

Specific Detailed Comments on the draft “A Conceptual Framework for U.S. EPA’s National Exposure Research Laboratory.”

Define the terms “stressor” and “receptor” at the very beginning of Section 2. It is not clear based on the definition of exposure as occurring “due to contact of a stressor with a receptor” (also as depicted in Figure 2-1) how the term “stressor” applies to a contaminant that is discharged into the environment and never comes into direct contact with a receptor but rather impacts the receptor indirectly by transformation or a series of food web processes. For example, is phosphorus a stressor or is the phytoplankton that it produces the stressor or is the low dissolved oxygen condition produced by phytoplankton sinking to the hypolimnion and decaying the stressor? Or, is it all of the above? In which case, the definitions of stressor and exposure must be modified. If the intent is to define exposure science broadly (and it seems that way from most of the text in the document), then the term “exposure” must comprise more than just direct uptake or contact with a receptor that produces a toxic effect, whether the receptor is human or another form of biota. It also would be useful to distinguish between a “pressure stressor” (sometimes called a “driver”) and a “state stressor.” With regard to the above example, external phosphorus loading would be a pressure stressor, whereas available phosphorus concentration within the system would be a state stressor.

Several places in the document refer to ecological receptors as being “individual plants or animals, communities of plants or animals, or entire ecosystems.” Ecosystem includes not only all of the organisms (including humans) in a defined space, but also includes the physical and chemical constituents and important biotic-abiotic feedback mechanisms within that defined space. Simply use individual organisms, populations, or communities, as appropriate and consistent with use of these terms by ecologists.

Another term that may have different meanings for different scientific groups, depending on their background, is the term “pathway.” To one of the NERLSS members, a “pathway” is a series of linked transport and transformation processes that connects—or produces exposure from—a stressor to a receptor. This is related to the definition of stressor and its place in the diagrams in Figures 2-3 and 2-4.

The concept of multiple stressors simultaneously affecting one or more receptors is important in exposure assessment. The potential for understanding the impacts of multiple stressors, whether multiple anthropogenic toxicants or multiple stressors spanning a range of physical, chemical, or biological stressors of anthropogenic and/or natural origin, is what makes exposure research so important. In that regard, the NERLSS suggests that the document take a broader view of multiple stressors than the one on page 5, which allows for multiple stressors to include “physical, chemical, and microbial agents.” The Subcommittee would argue that there are many biological agents that are not microbial that can be considered stressors; for example, invasive species, by definition, are considered as ecological stressors.

With regard to the text box that highlights the differences between human and ecological exposure, physical conditions often are the primary stressor of concern in ecological research

(e.g., previous evaluations of stressors by the EPA Science Advisory Board (Ecological Processes and Effects Committee [EPEC] identified hydrological changes and habitat degradation as more important than chemical or biological stressors), but chemical (excess nutrients and/or toxic substances) and biological (invasive species) stressors also are of concern. Research on impacts from multiple stressors acting in concert is critical to both human and ecological exposure research.

The paragraph below the text box on page 5, regarding the goal of exposure research, is very important and well-stated. One suggestion would be to bring out the concept of understanding the impacts of “multiple stressors acting in concert” as an important component of exposure research.

In the receptor box of Figure 2-3, the hierarchy of “community” and “population” can switch depending on the exposure systems being addressed (i.e., “ecosystem” or “human health”). This stems from the dual meaning of “community” in the two fields

For Figure 2-4, the same comment about community and population and the hierarchy applies.

It is very appropriate for this document to state that models are the underpinnings of exposure research (page 7) and to point out their value to both research and management. It might be good at this point to reference that NERL exposure research modeling can transition into management modeling and therefore, NERL will follow EPA’s draft document that presents guidelines for Regulatory Environmental Modeling (Draft Guidance on the Development, Evaluation, and Application of Regulatory Environmental Models, prepared by the Council for Regulatory Environmental Modeling, November 2003, and under revision after review by EPA’s Science Advisory Board [SAB]). Finally, the text box on page 8 really is a summary of management uses of models; NERL also might consider making a list of research uses of models, such as providing hypotheses and/or explanations of exposure pathways and synthesizing data collected on the state of a system into a system-level framework.

Figure 3-1 provides an excellent presentation of the overall Agency framework for protecting human health and the environment. It also does a good job of displaying the overlap between exposure and effects analysis. The following are some suggestions for making the diagram more consistent with previous comments:

- ✍ The labels on the ovals that represent stressors and receptors should be changed to “stressor(s)” and “receptor(s).”
- ✍ The circle labeled “Environmental Concentration/Condition” should be changed to “Processes and Conditions in the Receiving Environment.”
- ✍ On page 10, the document states that “risk to a receptor can only be reduced by reducing exposure.” The NERLSS would argue that there also are risk reduction actions that “reduce the susceptibility of the receptor.” Perhaps this concept can be worked into the diagram, and certainly this concept should be used in revising the first sentence in the section beginning, “How best to mitigate?”

Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and Resource Conservation and Recovery Act (RCRA) regulations should be added to the text box on page 12.

The text box on page 13 should insert the term “multiple” before stressors and sources. Also, with regard to the concept being presented here, there is a continuum of problems that range from “obvious what to do” to “obvious to do nothing.” All of the problems in between require some level of analysis, the complexity of which depends on the complexity of the system, the complexity of the questions being addressed, and the cost of potential regulatory/remedial actions to address the problem.

Section 4 should list, in order of importance, the criteria for prioritizing research development and implementation.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Gary Saylor", with a long horizontal flourish extending to the right.

Gary S. Saylor, Ph.D.
Chair, BOSC Executive Committee

Appendix A: BOSC NERL Standing Subcommittee Members

Subcommittee Members

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Appendix B: BOSC NERL Standing Subcommittee Charge

1. Effectiveness of the NERL Exposure Framework
 - (a) Please comment on the effectiveness of the Framework in describing the elements of exposure science.
 - (b) There are both similarities and differences in exposure science as it is applied to humans and ecosystems. Within the document, the authors tried to use concepts and terminology that could be applied to both disciplines with a discussion of differences only where necessary. Does the document provide a meaningful discussion for both disciplines? Are there recommendations for bridging the understanding of exposure research for both groups?
 - (c) Please comment on the effectiveness of the Framework in describing the uses of exposure science in furthering the Agency's mission to protect human health and the environment.
2. What are the core areas of expertise that are required within NERL to effectively conduct human health and ecological exposure research? How are these areas likely to evolve in the future?
3. How can we use the Exposure Framework as a communication tool?
 - (a) To enhance external communications?
 - (b) To develop new partnerships?
4. Please comment on the merits and barriers to conducting the exposure-related collaborative, multidisciplinary research that will be required to successfully address the full suite of risk assessment and risk management activities.

Appendix C: Framework Application Exercise

How would NERL apply the Framework to answer the following questions as applied to the charge provided in Exhibit 1?

- (1) Which elements represent research questions?
- (2) Which questions represent exposure science questions?
- (3) Which questions are definitely in NERL's expected domain?
- (4) Which questions may be shared between NERL and other ORD groups?
- (5) Which questions should be addressed outside of ORD?
- (6) For those questions that are definitely in NERL's domain, what would be the expected "product" of NERL efforts and to whom would the product be delivered?

Exhibit 1.
Information Needs to Define Concentrated Animal Feeding Operation (CAFO)
Waste Management Policy

CAFO Site Characterization

- ? Where are CAFO sites located?
- ? What type of animal feed operations are there? By location?
- ? What is the distribution of animal density?
- ? What is the ownership structure?
- ? What are the facilities? Core competencies? Profitability of their operations?

CAFO Waste Production and Management Characterizations

- ? What are the liquid waste production units? Solid waste production units?
- ? What are the quality characteristics of the liquid/solid waste streams?
- ? What are the waste management techniques in place?
- ? What are the waste disposal techniques in use?
- ? What are the nutrient loads and partitions in the various waste streams?

Ecological System Characterization

- ? Nutrient forms in the environment and mechanisms of nutrient transformation?
- ? Characterization of ecological system features and components?
- ? Location of ecological systems by characterization of features and components?

Ecological Impacts from Nutrients

- ? Ecological system components vulnerable and susceptible to nutrient exposure?
- ? Mechanistic progression of ecosystem response to nutrient exposure?
- ? Bioaccumulation pathway and mechanistic processes?
- ? Interdependence of ecosystem with other ecosystems?

CAFO Nutrient Fate & Transport

- ? What is the transformation process that nutrient species undergo in the various environments encountered on-site? Off-site?
- ? What is the bioavailability of the nutrient forms found in various stages of environmental fate?
- ? What is the biological uptake and processing of the nutrient forms found in the environment?
- ? Is there a concentrating effect of the nutrient within any population?
- ? What is the nutrient recycle process?

Nutrient Sensitivities Among Ecological Systems

- ? What ecological components have sensitivities or susceptibilities to nutrient content?
- ? What forms do the sensitivities take and what are the likely impacts on the susceptible specie(s)?
- ? What ecological components are impacted? What is the impact to the nutrient-susceptible components?
- ? Under what conditions and within which ecologies would those susceptible species be found?
- ? Are other chemical, biological, or physical conditions likely to be affected by the susceptibility of an ecological system impact?

National Projection of CAFO Nutrient Releases and Environmental Concentrations

- ? Integrated model of waterway hydrology, groundwater hydrology, nutrient release, nutrient fate and transport.

National Projection of Ecological Impacts from CAFO Nutrient Releases

- ? Integrated model of above CAFO nutrient releases and environmental concentrations with ecological system distributions, impact, and consequences.

Appendix D: Example Prioritization Algorithm

Several steps may help NERL improve the research planning and prioritization process in the future, and these should be evaluated for their suitability by NERL (Exhibit 2). Consideration of improvements, however, should not delay the publication of the current Framework for internal uses.

Exhibit 2. Research Prioritization and Planning Process Improvements

The prioritization of topics for Implementation Plans should be determined by a defined methodology that provides decisions makers with a clear outcome and reasonable documentation to justify the resulting priorities. The Agency's mission must be accomplished within the fiscal realities of NERL. The Framework should clearly state how NERL will prioritize its efforts along a return-on-investment continuum that addresses the expected value of the exposure-related research in supporting EPA's overall mission and programs. The table below illustrates one possible decision approach for prioritizing exposure-related research along a continuum of its expected value added. This value proposition can allow researchers and program administrators to quickly sort on those efforts that fall into the HIGH value category for subsequent prioritization. However, this approach needs to be modulated by the technical difficulties in such a qualitative risk comparison as noted by Cox, et al. (2005).¹ Furthermore, the cost of performing research in the HIGH category may be so high as to make performance of that research unrealistic.

Value Proposition of Exposure-Related Research for NERL Prioritization			
<i>A Priori</i> Suspected or Possible Exposure Levels vs. Outcome Threshold	Relative Measure of Uncertainty in Exposure (Exp) and Health Outcome (Out) Estimates for EPA Decision Support		
	Uexp >> Uout	Uexp ~ Uout	Uexp << Uout
Exposure Level Unknown	HIGH	HIGH	MOD
Exposure Level >> Threshold	HIGH	HIGH	MOD
Exposure Level ~ Threshold	MOD	MOD	LOW
Exposure Level << Threshold	LOW	LOW	LOW

The obvious conflict in prioritization practices is the apparent independence of the Implementation Plans developed in response to the overall agenda of EPA. To garner greater coherence of the planning process for NERL, routine systemic reviews of all Implementation Plan requirements are necessary. The annual budgetary reviews must require this type of comprehensive assessment across all Implementation Plans, but are the synergistic opportunities available to NERL understood during the review process and can they be understood using the

¹ Cox, L.A, D. Babayer, W. Huber, Some limitations of quantitative risk rating system, Risk Analysis, 25(3), 651-662, (2005).

current practices? It would seem that a more extensive planning process every 3 to 5 years may be required by NERL to align: (1) skill set requirements for NERL staff; (2) research capacity to be built and how to build it (e.g., internal vs. external, location, generalizable domain knowledge or specific program application, etc.); (3) updates and modifications to the Guidelines or NERL standards of practice that could influence research directions; and (4) expert opinion on the mission critical drivers for exposure science research.

Appendix E: List of Acronyms

BOSC	Board of Scientific Counselors
CAFO	Concentrated Animal Feeding Operation
CDC	Centers for Disease Control and Prevention
CMAQ	Community Multiscale Air Quality
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
EPA	U.S. Environmental Protection Agency
GI	Gastrointestinal
IP	Implementation Plan
MYP	Multi-Year Plan
NERL	National Exposure Research Laboratory
NERLSS	NERL Standing Subcommittee
NHEERL	National Health and Environmental Effects Research Laboratory
ORD	Office of Research and Development
PI	Principal Investigator
PM	Particulate Matter
QA/QC	Quality Assurance/Quality Control
RCRA	Resource Conservation and Recovery Act
SAB	Scientific Advisory Board
SDWA	Safe Drinking Water Act