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July 20, 2005

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Mr. E. Timothy Oppelt  
Acting Assistant Administrator  
Office of Research and Development  
U.S. Environmental Protection Agency  
Washington, DC 20460

Dr. Robert Kavlock  
Director  
National Center for Computational Toxicology  
U.S. Environmental Protection Agency  
Research Triangle Park, NC 27711

Re: National Center for Computational Toxicology Review

Dear Mr. Oppelt and Dr. Kavlock:

This is a letter report from the Board of Scientific Counselors (BOSC) reviewing the progress of the new National Center for Computational Toxicology (NCCT). Dr. Kavlock and his staff at the NCCT presented an overview of the Center's structure, activities, goals, and progress on April 25-26, 2005, to a Subcommittee of the BOSC. The Subcommittee consists of Drs. George Daston (Chair), James Clark, Richard DiGiulio, Michael Clegg, and Ken Ramos. Dr. Clegg was unable to attend the briefing and Dr. Ramos recused himself because of a potential conflict of interest.

Because the NCCT is so new, becoming operational in February 2005, this report is a prospective one, and is intended to be the first of several consultative reviews of the Center's progress. In particular, we concentrate on NCCT's strategic goals; its collaborations, and connectedness to the rest of the Agency and to outside scientists; its staffing plan; and its thematic choices. We addressed a number of charge questions intended to focus on each of these areas. Those charge questions and the Subcommittee's responses are listed below, following some general comments about the Center.

The Subcommittee was extremely impressed with the progress NCCT has made in the few short months of its existence. NCCT's mission is to serve as a focal point for the U.S. Environmental Protection Agency (EPA) in the application of mathematical and computational tools to all facets of the risk assessment process. To be successful at this, the NCCT must: (1) provide a critical mass of expertise in computational, mathematical, and statistical modeling; (2) develop research collaborations and partnerships with a large number of groups within and outside the Agency; and (3) have a clear understanding of and regular interactions with its customers in the rest of the Office of Research and Development (ORD), the program offices, and the regions. The Center already has made considerable progress on all three fronts.

Because its staffing is limited, NCCT has made the appropriate choice of concentrating on gathering staff with biological, chemical, and statistical modeling expertise rather than on a particular biological or chemistry

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specialty. This is an appropriate choice, as the staff is strongly aligned to the mission of the Center. The composition of the staff is impressive; it includes some of EPA's most accomplished biological modelers, chemists, and statisticians. Most of these individuals have strong track records of collaboration with multiple laboratories and already are sought after as research partners. This choice of personnel automatically leverages NCCT's potential well beyond what would normally be expected of a group of 19. NCCT has created a virtual organization that brings these people together in a way that allows them to synergize and form ad hoc groups to make progress on multiple fronts simultaneously.

The Center already has collaborations and programmatic augmentations via internal and Science To Achieve Results (STAR) grants. These partnerships cover a large number of areas of modern biology and chemistry that require high-powered computational and/or modeling expertise, such as genomics, proteomics, and metabonomics, with coverage of mammalian toxicology, ecotoxicology, microbiology, exposure assessment, and quantitative risk assessment. NCCT has a steering committee—the Computational Toxicology Implementation and Steering Committee (CTISC)—that represents ORD laboratories/centers, program offices, and regions. The role of the CTISC is still evolving and it will be an important avenue for communication and for identifying possible partnerships.

NCCT's strategic plan includes deliverables with short- and longer-term time horizons. Emphasis on Information Technologies, Prioritization Tools, Biological Models, and Cumulative Risk will take advantage of the Center's strengths and provide much of the Agency with technology that will improve its ability to fulfill its mission. It is clear that the Information Technologies (especially DSSTox) and Prioritization Tools (especially ToxCast) have the potential to address significant issues in toxicology data management and prioritization for testing.

### **Charge Questions and Responses**

Questions for the Center as a whole:

- 1. Success of the NCCT will depend upon establishing effective collaborations with the other ORD laboratories and centers. What advice can you provide to ensure that operations remain integrated with the other laboratories and centers within ORD?*

The Subcommittee members believe that NCCT has been set up in an optimal way to maximize interactions, by concentrating expertise in modeling within the Center, rather than the toxicologists, risk assessment specialists, etc., who populate the other laboratories and centers. This provides a natural focus area on which the other laboratories and centers will seek collaboration. Furthermore, most of the staff at the Center are highly experienced and have a long history of successful collaborations, including a number of active collaborations that they bring with them. The staff is a natural magnet for collaborations.

One challenge will be to transition the Center from a collection of experts in various fields to a center of excellence in applying the broad tools of computational toxicology to address the human health and environmental health issues under the purview of EPA. Experts will need to develop procedures to capture the essence of thought processes and computational tools that can be applied to the diversity of challenges the Agency addresses. Many of the Center staff will be required to shift their focus from finding computational approaches to address a set of specific issues to developing robust tools and procedures that provide computational frameworks that support ORD and Agency programs.

Not all the modeling expertise within EPA resides within NCCT, let alone the disciplines that rely on computational toxicology. The Center should consider forming an informal “community of practice” within EPA that can serve a networking function for interested scientists. This community of practice would not be an administrative unit, but a virtual professional society within the Agency. Most of its business can be conducted via electronic media, with occasional meetings. The Subcommittee endorses the Center’s concept of trying to develop various personnel alignments and management tools (e.g., appointing agency/federal/academic scientists as adjunct or associate faculty of the Center) to help recruit or gain input from a broader number of scientists. Those individuals with technical expertise aligned with the Center’s activities can be encouraged to contribute to NCCT activities while being housed in other organizations within ORD, EPA, or outside of the Agency; they will form the nucleus of the community of practice.

The CTISC should be explicitly tasked with identifying possible partnerships and collaborations (and of prioritizing them, if necessary). ORD should continue to hold regular meetings of its Laboratory and Center Directors, at which partnerships among centers, including NCCT, can be explored.

The internal grant program that supports many of the NCCT collaborations is important and likely to be highly successful. Future grant programs should provide a preference for projects that collaborate with the Center.

Finally, NCCT should develop a communications plan to share its accomplishments and capabilities with the rest of EPA and those external to the Agency.

- 2. In terms of anticipated staffing, are there particular areas that should receive greater or lesser attention?*

NCCT may wish to consider adding one or two staff who have expertise in bioinformatics. The planned grant for an external bioinformatics center will cover most of the Center’s needs in this area, but having some internal expertise would complement the external bioinformatics efforts and provide a natural point of contact between the external group and NCCT. The Center also should consider whether there are social science applications to computational toxicology, and if so, whether there is a social science expertise that should be represented on the staff.

NCCT also may wish to consider hiring one or two leading scientists in the field of ecological modeling. Of the many competencies that could be targeted, fields such as modeling large-scale ecological processes, population and community dynamics, tissue dynamics in ecological receptors (PB/PK, bioaccumulation processes, and lethal/adverse effects of body burdens), and environmental fate and effects of chemicals (including microbial biodegradation and bioavailability) would be particularly useful. Although it is unlikely that one individual will have expertise spanning all these areas, having an individual with modeling expertise will serve as a focal point for collaborations with EPA scientists outside the Center who have complementary expertise. During the review, the Center staff demonstrated the importance of obtaining insight from social scientists in developing technically sound and meaningful studies. NCCT should consider including this area of expertise among the core competencies of the Center.

- 3. As we find ourselves in the post-genome era, science is progressing at a rapid pace. This makes it difficult to stay abreast with the current state-of-the-science. Clearly, being cognizant of and understanding the technologies and advanced methods in the areas of the omics, modeling, and statistics is a considerable vested interest to NCCT for several reasons, such as being able to make decisions about which technologies are best for the Center to pursue and most beneficial to the Agency. Can the BOSC provide any suggestions on how best to keep apace with new technologies and methodologies?*

This is a problem that we all face, but is perhaps more severe for an integrating group such as NCCT. Partnerships with other organizations with similar/complementary interests may be the best way to facilitate keeping current. Active collaborations, which already are the stock-in-trade for the Center, publication, and participation in professional meetings will keep the Center staff fresh and well informed. These efforts also will serve to attract the brightest students and post-doctoral fellows, who will bring with them the latest technologies.

Questions concerning the areas of emphasis, or “Concept Topics”:

- 4. Has the Center articulated a clear rationale for each topic area, and has it provided evidence that the contemplated approaches will be able to address the major goals stated in A Framework for a Computational Toxicology Research Program?*

The Subcommittee members believe that NCCT is on track. It will be important for the Center to prepare a synthesized set of goals/milestones for the numerous projects in which the Center is involved, explaining how each fulfills a need, and how each topic area will provide tools for the Agency. The prioritization process that the Center leadership has developed is a good one, which works well in selecting program areas that are consistent with the Center’s mission.

5. *To be successful in addressing the Concept Topics, can you help identify potentially fruitful partnerships with others outside the Agency?*

The review provided plenty of evidence that the Center is reaching out to find potential collaborators among a diverse set of U.S. government and private institutions. Many of the collaborations discussed should be formalized in Memoranda of Understanding (MOU), Interagency Agreements (IAGs), and other formal commitments to demonstrate the degree of cooperation, leverage, and interest generated with other partners. Also, NCCT will need to have opportunities to work with scientists and regulatory authorities from countries around the world, as computational toxicology is an area of evolving science with expertise in Europe, Canada, Asia, perhaps Russia, as well as the United States.

One approach to broaden international contacts would be to consider development of ties with U.S.-based academic centers and institutions that have liaisons with international scientists and organizations. Also, Center management may want to specifically reserve some travel allocations to allow attendance at conferences, workshops, or technical exchanges and site visits at leading international sites and organizations around the world. A world-class center will need worldwide perspectives in computational toxicology.

NCCT already is doing a good job of establishing liaisons with other organizations involved in aspects of computational toxicology, such as the National Center for Toxicogenomics at the National Institute of Environmental Health Sciences (NIEHS). Efforts should be continued to partner with private industry in areas of mutual interest.

6. *Given the mission, staffing, and resources of the Center, what is your view of the depth and breadth of the areas currently selected for emphasis? Are there additional areas that should be considered?*

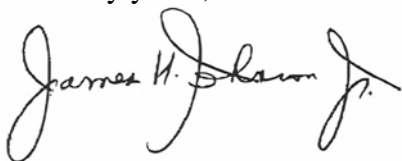
The Subcommittee members believe that the Center is doing a good job of maintaining broad coverage through its collaborations with multiple laboratories. Depth will come from the other laboratories and programs with which NCCT collaborates.

The Center's goal to take advantage of opportunities to broaden and generalize the technical approaches to the diverse scope of Agency issues is an admirable goal, and one that will require a disciplined approach among the technical and managerial team to implement. The Subcommittee realizes that the endocrine disruptor studies offer many concrete examples of the kind of molecular and cellular work the NCCT can provide in the future. It will be important that the Center quickly provides similar services and value to EPA programs that can benefit from these tools applied to non-endocrine disruption issues. Plans to broaden program office representation in the CTISC (to include the Offices of Solid Waste and Emergency Response and Homeland Security, and possibly others) should quickly bring these opportunities to

the forefront. Discussions should proceed with Agency programs and offices dealing with waste management and issues surrounding remediation of contaminated sites; applications of environmental models to total maximum daily loads (TMDLs); environmental health monitoring programs such as the Environmental Monitoring and Assessment Program (EMAP), various regional Bay programs (Chesapeake Bay, Great Lakes Program, Florida Everglades), as well as the air and water monitoring programs conducted by the states with federal assistance. Understanding the chemical and biological stressors encountered in these environmental health studies will broaden the types of contaminants and thus computational tools that must be considered by NCCT. It also will challenge applications of the Center's tools to issues with a broad temporal and spatial scale and provide opportunities to assess some dynamic aspects of human and animal populations.

In conclusion, the BOSC Subcommittee believes that NCCT has made great progress and is on the right track to deliver against its mission. We are pleased to provide advice on this important Center and look forward to our continuing oversight of NCCT.

Sincerely yours,

A handwritten signature in black ink, reading "James H. Johnson, Jr." in a cursive script.

James H. Johnson, Jr.  
Chair, Board of Scientific Counselors