September 16, 2008

Dr. George Gray
Assistant Administrator
Office of Research and Development
U.S. Environmental Protection Agency

Dr. Robert Kavlock
Director
National Center for Computational Toxicology
U.S. Environmental Protection Agency

Dear Drs. Gray and Kavlock:

This is a letter report from the Board of Scientific Counselors (BOSC) reviewing the National Center for Computational Toxicology (NCCT). The Computational Toxicology Subcommittee of the BOSC Executive Committee reviewed NCCT's progress and plans during a 2-day meeting held December 17-18, 2007, at the EPA facility in Research Triangle Park, North Carolina. The BOSC Subcommittee consists of George Daston (Chair), James Clark, Richard DiGiulio, Muiz Mumtaz, John Quackenbush, and Cynthia Stokes.

This is the third review of NCCT conducted by the BOSC. The Subcommittee was very pleased with the progress that the Center has made towards its goals. NCCT first became operational in February 2005; during the 2.5 years between its establishment and this review, NCCT has made substantial progress in establishing priorities and goals; making connections within and outside EPA to leverage the staff's considerable modeling expertise; expanding its capabilities in informatics; and making significant contributions to research and decision-making throughout the Agency. We are pleased to see that informatics tools developed by the Center already are being used by program offices, and that the program offices are taking advantage of the expertise of the Center in developing critical elements for risk assessment, such as a biologically-based dose-response (BBDR) model for arsenic, an environmental contaminant of considerable public health importance. Many of the recommendations made by BOSC during its earlier reviews have been acted on by NCCT. This includes improved capabilities in bioinformatics through the funding of two external centers and in informatics and systems biology through staff hires; expansion of its

technical approaches to even more programs within the Agency; and the formation of an extensive collaboration with the National Institute of Environmental Health Sciences (NIEHS) and the National Human Genome Research Institute (NHGRI) for its ToxCast project.

The purpose of the December 2007 review was to continue to provide NCCT with advice on the progress the Center has made, in the past year, in fulfilling its mission and strategic goals. In particular, the Subcommittee addressed six charge questions for five NCCT activities (ToxCast, Informatics Technology/Information Management (IT/IM) activities, Virtual Liver, Developmental Systems Biology, and Arsenic BBDR). The Subcommittee's responses to these questions follow.

Charge Question 1: *Does the scope and involvement of expertise in the project reflect activities consistent with the function of a Center?*

The NCCT was founded only a few years ago and has been achieving a critical mass of expertise through selective hiring, external grants, and the formation of connections with other groups of experts within EPA. The purpose of this question was to gauge the progress of the Center in achieving the level of expertise needed to pursue its mission.

The staff working in NCCT and those scientists involved from outside the Agency who are working as collaborators are highly qualified in various aspects of computational toxicology. The Center's effort to solidify formal agreements in terms of memoranda of understanding (MOUs), cooperative research and development agreements (CRADAs), etc., with various organizations has opened up a diversity of quality opportunities to leverage and enhance Office of Research and Development (ORD) efforts. A timely example is the February 14, 2008, announcement of the collaboration between NIEHS, NHGRI, and EPA's NCCT. As described in the press release, this collaboration leverages the strengths of each group to use high-speed, automated screening robots to test suspected toxicants using cells and isolated molecular targets.

The staff and collaborators at the center have the appropriate expertise and insights. The utility of the tools and deliverables can be enhanced if the staff moves toward being more explicit on how the tools under development support EPA risk assessments. Some of the ORD researchers seem to be searching for an application for their sophisticated tools, and discussions with Agency staff practicing risk assessments (Office of Pollution Prevention and Toxics [OPPT]; Office of Water, Office of Wastewater Management; Office of Prevention, Pesticides, and Toxic Substances [OPPTS], etc.) could provide direction as to the appropriate milestones and deliverables for these efforts. The BOSC reviews and the Center would benefit if representatives from these Agency offices attended BOSC reviews to ensure that all parties understand how NCCT's efforts address the most relevant needs of the Agency. The BOSC wants to ensure that this advice is seen as encouragement to reach out to risk assessment practitioners. The ongoing work in developing the analytical approaches and information databases is of high technical quality, as the Center staff and collaborators are working on many new and exciting approaches. By holding research planning discussions with risk assessment practitioners, the applications of the computational toxicology tools and resources can be directed to ensure the most relevant and efficient use of data and models.

One challenge for the center staff involved in developing informatics datasets will be to develop efficient and effective ways to handle the wealth of data available in some areas to avoid redundancies of data entries and to focus on the most informative data. Again, interactions with various program offices and their risk assessment activities should provide a basis to set the long-term goals for the Informatics/Data management team. This will allow the development of structured short-term and mid-term activities needed to meet the long-term goals.

The BOSC noted that it remains somewhat unclear how the Center intends to use ToxCast and associated analyses to approach risk assessment. For instance, species-to-species translation was mentioned, and the data are being obtained from multiple species, not just humans, but how the different species data will be reconciled was not discussed. Although the primary goal of the ToxCast project is prioritization of chemicals for detailed risk assessment, not the risk assessment itself, it is interesting to contemplate how the projected database and analysis might be directly relevant. Similarly, it was noted that an early decision regarding ToxCast was that ecology and paths of exposure were not going to be addressed in this project (at least not initially). Nonetheless, at several points, paths of exposure arose during the review because of their obvious relevance. The Subcommittee is prompted to ask how it might be addressed in future work.

The Subcommittee also noted that the means of using the eventual Virtual Liver models for actual risk assessment at EPA is unclear. The BOSC encourages additional thought and efforts along these lines, in collaboration with the appropriate EPA program office personnel. This is not a criticism of the current project vision by any means, but because direct or indirect application to risk assessment would be a fantastic result, it seems prudent to consider the possibility earlier rather than later.

Charge Question 2: *Are the goals and milestones suitably described, ambitious, and innovative?*

The purpose of this question was to determine whether NCCT is performing its mission of providing novel approaches to the practical problems of toxicology and risk assessment that are needed by EPA.

For the Center overall, the answer to this question is “yes.” In particular, the goals of the Center are well-described, very ambitious and innovative, as well as important for the future of research at EPA. The issue of “milestones” is somewhat more complex, in part due to the varying levels of maturity for Center components. In most cases, previous accomplishments and current activities are well described, but more detail concerning projected future milestones would be helpful. It is recognized, however, that these projects are very innovative and substantial flexibility is appropriate. This is particularly true for less mature but highly creative projects such as the Virtual Liver and Virtual Embryo. Also, in considering goals and milestones, it may be appropriate to consider the timely integration of each project’s accomplishments into the Agency’s risk assessment activities. In the following paragraphs, Charge Question 2 is addressed in the context of the five major Center activities discussed at the review meeting.

ToxCast. ToxCast is the most mature of the Center's projects, which is appropriate considering that it is most central to NCCT's overall mission. The goal of this project, to provide a cost and time-efficient methodology for screening and prioritizing chemicals of concern to the Agency (~11,000 by current estimates) is suitably ambitious, and is well described. Progress on this project has been very strong and these accomplished milestones are very well described. Future plans for the project also are well described, although a more detailed time table for milestones past 2008 would be helpful.

IT/IM Activities. This project is highly symbiotic with ToxCast, and the success of one is highly dependent on the success of the other. By extension, the success of the NCCT overall depends upon the success of these two projects. The comments above for ToxCast also pertain to the Informatics project. The project is highly and suitably ambitious, and its goals and substantial progress are well described. Again, future plans are described well in a general way, but more detail concerning future milestones (beyond 2008, which is well described) would be appropriate.

Virtual Liver. Although narrower in scope than the foregoing projects, the Virtual Liver project is very ambitious; it also is relatively young, apparently becoming fully operational with the arrival of Dr. Imran Shah in September 2006. Its fit with the goals of NCCT is perhaps less clear than the previous two projects; it is more "visionary" in nature, and less directly applicable to risk assessment, as described by one of the EPA scientists involved. The goals of the project and the nature of research to be performed to achieve those goals are clearly described. There is some concern that this project may be overly ambitious. It may be helpful if key objectives were delineated and prioritized, perhaps indicating achievements that are critical to the success of the project and those that are highly desirable. Milestones for tracking the project's progress are not apparent, particularly in later years (3-5). This relatively young and very innovative project requires considerable flexibility, however, so the lack of detailed milestones in later years is very reasonable.

Developmental Systems Biology (Virtual Embryo). This project is at a substantially earlier stage than the Virtual Liver project; it is led by Dr. Thomas Knudsen who joined NCCT in September 2007. The issues of goals and milestones are essentially the same as for the Virtual Liver, that is, strong on the former, but understandably weaker on the latter. It is the Subcommittee's expectation that a more concrete research plan with goals and milestones will be developed over the coming months.

Arsenic BBDR. This also is a relatively new effort, with planning beginning in 2006. This project is unusual among NCCT projects in that it is oriented toward a specific chemical with a specific issue (Safe Drinking Water Act revisions) rather than an approach developed with diverse chemicals in mind. However, this project is likely to inform the eventual development of other biologically-based dose-response models and their application to risk assessments by the Agency. Thus, in addition to informing the controversial issue of arsenic risk assessment, the project is more broadly relevant to the mission of the NCCT. The goals of the project are very clear and well described. Milestones, however, are not stated, and may be particularly important for this project, which has a clear deadline (2011) in order to be useful for the 2012 Safe Drinking Water Act review cycle.

Charge Question 3: *Are there significant gaps in the approach that can be pointed out at this point in the evolution of the project?*

ToxCast. Dr. Dix and the ToxCast project contributors are commended for their progress in this activity in terms of specification of desired data and the contracting of various entities to obtain these data. The data acquisition is clearly well under way. The main gap noted is relevant to both the ToxCast and IT/IM activities. Specifically, the Subcommittee notes that the structural specification of the database for compilation and rigorous quantitative analysis of the ToxCast data remains unclear. Because the data types are highly heterogeneous and the dataset is very large, developing these structural specifications will be a challenge that the Subcommittee suggests should be addressed as soon as possible. The IT/IM team acknowledges that this area is a significant challenge (e.g., the description in the write-up provided to the Subcommittee prior to the review meeting). One suggestion is that the ToxCast team compile a list of some specific use cases, for example, specific questions that they intend to address with the database. This will help make concrete the needed database attributes that will allow the analysis for the chemical prioritization that is the end goal of the ToxCast project.

IT/IM Activities. The IT/IM activity group has clearly made significant progress since the last BOSC Subcommittee meeting in terms of specification and development of various software and database tools for storing and accessing various toxicology data in existence as well as being generated (e.g., in the ToxCast project). The fact that their ToxRef database and utility are being used already by the Office of Pesticide Programs to retroactively explore its own data demonstrates early utility and applicability beyond tNCCT itself. The major gap noted for this activity was described in the ToxCast project section above. In addition, finding an efficient and effective methodology for extracting data from text sources was a concern for the Subcommittee. A trial of natural language processing (NLP) for pulling information into some of the databases was described. The Subcommittee notes that this method has been attempted rather unsuccessfully by various research groups over probably 2 decades and thereby encourages the exploration of other possible approaches as well.

Virtual Liver. Dr. Shah and his group are commended for having good command of the significant breadth of biology, toxicology, and modeling that impact the project. In addition, the "big picture" vision described is useful—there are many important questions in the field and not limiting the vision too early is appropriate. The Subcommittee believes that this should be balanced, however, with some very specific goals, milestones, and timelines for the next few years that are clearly attainable with the resources at hand in order to assure some useful concrete outcomes. In a project with this possible magnitude, it can be tempting to try to do everything, both in terms of the various project approaches (knowledgebase (KB), biological modeling, dosimetry modeling, etc.) as well as the scope within any one approach (breadth of the KB, breadth and detail of every model, etc.), and thereby end up with little actually completed. One suggestion is that Dr. Shah and the group develop a short prioritized list of specific scientific research questions relevant to EPA's goals that they desire to address as soon as possible, and use this to focus first iterations of development of both the KB and model(s). More explicit milestones and goals for these highest priority questions then can be developed. Later iterations of KB development and modeling can add scope (breadth/depth) to allow NCCT to address

additional research questions. The Virtual Liver activity will result in models of parts of the biology being developed simultaneously and presumably by different individuals. Because the idea is to integrate these models eventually to predict effects from molecular function to physiologic outcome, the compatibility of the models is paramount. Dr. Shah indicated that he is cognizant of and planning to manage this issue, for instance, by looking into the efforts of the international Physiome Project. The Subcommittee members note that, to their knowledge, the issue of common coding language, which has been addressed quite extensively by the Physiome Project, does not appear to have addressed more subtle but critical compatibility issues concerning biological and mathematical specifications among models, such as compatibility of assumptions, equilibrium approximations, time scales, and so forth. Hence, beyond managing compatible coding, the activity group is encouraged to actively plan for and manage on an ongoing basis the specifications that must be shared among models so as to produce compatibility when it is needed.

Developmental Systems Biology (Virtual Embryo). This project is very early in its development, and already shows interesting progress based on the continuation of the earlier work by Dr. Knudsen. Because the data needs of the proposed models may be significant, the Subcommittee notes that it will be critical to identify and enlist appropriate supporters and collaborators to provide such data. The track record of the principal investigator suggests that this will develop naturally.

Arsenic BBDR. No specific technical gaps in the approach were noted for this activity. Because the goal is to use the project's resulting model(s) for the 2012 review cycle of the Safe Drinking Water Act, the Subcommittee encourages continuous communication with the appropriate program office personnel so that concerns, objections, and skepticism can be addressed early and on an ongoing basis. The group is commended for having such communication already in place and it is encouraged to maintain that communication to the greatest degree possible.

Charge Question 4: *Does the work offer to significantly improve environmental health impacts and is the path toward regulatory acceptance and utilization apparent**?***

This question was included so that the Subcommittee could provide an opinion as to the potential for NCCT's research to impact decision-making by the programs and offices that administer regulations that are important for public and environmental health.

The Subcommittee believes that the work being reviewed has the potential to significantly improve a number of aspects of the risk assessment process, and in so doing will lead to substantial improvements in environmental health. As noted in the responses to previous questions, the programs under review are at different levels of maturity and will deliver results at different time points. The potential to improve the public and environmental health protection role of the Agency, however, is enormous. These improvements will come in the form of better tools for the prioritization of chemicals to evaluate and assess, early insight into the potential toxicity of new substances by improved capabilities of searching for structural analogs for which data already exist, better understanding of the fundamental molecular processes that underlie toxicity and variability in response, and better methods for incorporating that information into risk assessment. As with the other responses, each project that was reviewed will be discussed in

separate paragraphs below (with the exception of the Arsenic BBDR, which will be addressed under Charge Question 4a).

ToxCast. This project already has begun to generate a considerable database on the cellular and biochemical effects of approximately 300 well-studied chemicals, mostly pesticides. The advantage of choosing this set of chemicals, nominated by the Office of Pesticide Programs, is that they already have been assessed for their potential to cause toxicity using a comprehensive set of toxicity tests. This will provide the phenotypic anchoring for responses that are observed in the high-throughput and other test methodologies that ToxCast is employing. ToxCast has the goal of providing a scientific foundation for predicting the potential hazards of chemicals by evaluating the responses of relevant molecular and cellular markers in simpler experimental systems. This will lead to an improved ability to prioritize testing, better test methods, testing strategies that are tailored to the chemical being tested, and perhaps ultimately to the replacement of existing test methods with ones that are not encumbered with much of the uncertainty inherent in traditional toxicity tests. In order to reach this potential ToxCast will need to generate a lot of new data. The recently announced collaboration between NCCT, NIEHS, and NHGRI will accelerate progress in this area and is a wise use of limited resources.

IT/IM Activities. The database and software development has been outstanding. ToxRef already is in use at the Office of Pesticide Programs and is allowing toxicologists and risk assessors to query large databases of chemical structures for common toxicological properties. Relational databases of this type provide novel opportunities for risk assessors to consider the potential biological activity of new chemicals instead of just production volume (or other surrogates of potential exposure) in prioritizing them for further evaluation and testing. This already is a major achievement with practical applications.

Virtual Liver and Virtual Embryo. These programs have longer time horizons but have significant potential to improve risk assessment. The liver is a common target organ for toxic agents, and is a primary site of metabolism of xenobiotic compounds. Adverse effects on embryonic development usually are irreversible, and the economic and emotional consequences of adverse developmental outcome are significant. Therefore, the choice of these two systems for intense investigative and modeling approaches is appropriate for an agency interested in the public health consequences of toxicant exposure. As noted in previous responses, these programs will need to progress a little farther before enough of a scientific foundation is created to accurately determine how they will be incorporated into the risk assessment process. It already is clear that the information being generated will be important in reducing the uncertainty associated with determining which chemicals pose hazards, variability in susceptibility in a heterogeneous population, and other critical questions.

- ***Charge Question 4a:*** *In addition, specifically for the Arsenic BBDR project: Does the proposed computational model have the potential to identify and reduce uncertainties with the risk assessment process?*

The answer to this question is yes, depending on data gaps identified and resources made available. This study might not give all the answers but will get us halfway there. EPA recognizes that developing a universal arsenic model describing several cancer endpoints is a

formidable challenge. Hence a step-wise research project with an eye for the future is proposed. Initially, a generic model for cancer will be developed that will incorporate key steps of the mode of action commonly shared for multiple cancer types such as oxidative stress. This model, in turn, will serve as an engine to develop specific cancer models as the need arises and resources become available. To ascertain whether appropriate steps are being incorporated, a thorough literature review of experimental and epidemiological data and expert consultation has been proposed. It also is acknowledged that even though there is a lot of data, they are somewhat weak to generate exposure time course response curves. Appropriate experiments have been proposed to fill the research needs to develop a realistic model.

- ***Charge Question 4b:*** *Will the model be able to help identify susceptible populations and compare potential risks in those populations with less susceptible populations?*

Yes, the initial generic model development exercise will allow identification of issues such as mechanisms that operate in general versus subpopulations, such as susceptible populations with varying degree of arsenic methylation. Such issues could be the subject of workshops to explore the issue of the extent of polymorphism in the human population.

The short-term (1-2 years) goal is the establishment of a coordinated program of laboratory research to generate essential data needed to develop a BBDR model that will increase confidence in the predictions. To start with, the model development will be initiated with available data. Work proposed includes multistage clonal growth modeling, target tissue dosimetry, and methylated metabolites of arsenic.

The long-term (3-5 years) goal of developing a robust version might be too optimistic. As the project gets underway, new questions and issues might be identified that will require additional laboratory research and continued resources. The project has a good future as it can be easily adapted to the latest (2007) National Academies toxicity testing report that recommends a systems biology and computational tool integration.

- ***Charge Question 4c:*** *Is coordination between model development and associated data collection sufficient to avoid problems with models being either over- or under-determined?*

Yes, it is desirable to see what health effects are caused at lower doses to avoid the potential of compromise in setting an arsenic standard based on cost-benefit analysis.

Charge Question 5: *Have appropriate data management and analysis tools been incorporated into the project?*

Previous reviews have highlighted the importance, as well as the challenges, of developing useful relational databases. This question was included so that the Subcommittee could evaluate the Center's progress in developing and implementing strategies for data management and analysis.

ToxCast. With regard to ToxCast, NCCT has made great progress in the past 18 months in hiring bioinformatics and computational biology scientists and staff members to establish the

infrastructure necessary to begin meeting the needs of the program. The challenges here also are the strengths of the ToxCast: the diversity of the data that it will generate and the need to effectively organize that information to facilitate its analysis and interpretation. The approach taken by Dr. Richard Judson and his group is a sensible one given the state of the field: information from each technology with which data will be generated will be captured in a technology-specific database, and this information ultimately will be collected in a central data warehouse linking the information together. The advantage of this solution is that it allows the data from each assay to be stored in a rational format while deferring the question of how the information will be combined to address questions relevant to the mission of EPA.

The construction of the warehouse remains an open question. Ultimately, a database is a model of the interactions that exist in the underlying data and the relationships relevant to the analysis that will be performed. The diversity of the data, representing a wide range of *in vivo* and *in vitro* assays from multiple species, makes building such a model a significant challenge. The project seems to be lacking a set of analytical objectives necessary for building the relevant use cases that ultimately will inform the process of database construction, and this ultimately will determine its utility. At this stage, ToxCast needs to begin to define analytical outcomes in order to set goals and milestones with regard to developing and validating analytical protocols. This is an essential step at this point as it will help to anchor future development and make it relevant. This also will help to define the requirements of the interfaces that are built to access the data.

Further, the ToxCast group should be encouraged to release the data and databases at the earliest possible time and to consider a "CAMDA-like" workshop in which the research community is offered access to the data with the challenge of using the data to effectively predict end points. At least three advantages to the program will be derived from these efforts. First, public release will help to drive the creation of relevant use cases that will further database development. Second, it will assist in evaluating data access protocols and tools to assure the greatest utility to the research and regulatory community. Third, it will accelerate the development of predictive algorithms to combine the data to make predictions about relevant phenotypic outcomes.

Virtual Liver. The Virtual Liver is a very ambitious project designed to simulate molecular, cellular, physiological, and organ-level computational models that ultimately can be used to make predictions regarding the toxic effects of various compounds. To limit the scope of the project to something that might be manageable, its initial focus will be nuclear receptor-mediated non-genotoxic liver cancer. The group should be applauded for this decision as it will give staff the opportunity to focus enough to make progress.

The starting point and first challenge will be the construction of a liver KB. In any domain, this is a nontrivial problem and ultimately will require linking information in the literature and a host of public data resources. The use of publicly available resources and tools and the commitment to making the KB available are commendable not only because it will be widely useful to the broader community, but also because it will accelerate the development and curation of the information within the KB.

With regards to populating the KB, the use of NLP probably is not the best solution. NLP does not work well with the scientific literature, and its application in this domain remains an area of

active research. Application of NLP has the potential to introduce a great deal of noise in the system, leading to many potential false associations that could lead to more problems than it solves. Consequently, other methods, including expert or community curation, should be explored.

On a larger scale, the greatest potential problem will be linking each of the domain-specific models to build a predictive system. Again, this remains an area of active research and one that may present significant barriers to developing verifiable solutions. The greatest challenges will be to validate any models that emerge from the analysis.

Finally, there is a need to develop standards for interactivity and try to interface with developing standards within the community.

Virtual Embryo. This project is in its early stages, with Dr. Knudsen only having arrived 3 months prior to this review. As such, it is still not well integrated with the overall NCCT program, and in particular ToxCast. It remains to be seen how well it will eventually integrate with the overall program, and its integration with other internal and external initiatives needs to be resolved. Nevertheless, it appears that this project could provide an opportunity to explore the results emerging from ToxCast, and it may help direct selection of the next generation of compounds for analysis in ToxCast.

Charge Question 6: *How would you assess the outreach to other groups in executing the projects?*

Because of NCCT's limited size, it is vitally important that the Center be connected in meaningful ways to other groups of experts who can augment the Center's capabilities. The purpose of this question was to determine the Center's progress in making and leveraging connections.

NCCT has done an admirable job in reaching out to other groups, both inside and outside the Agency. Because of the relatively small size of the Center, outreach is important as a way of augmenting its productivity. Outreach also is important in engaging others in understanding the capabilities of computational toxicology, which will be crucial in convincing program offices to use the tools developed by the Center. NCCT is doing a good job on both counts.

NCCT has been successful at developing partnerships at several levels. Within ORD, NCCT has developed successful partnerships with the National Health and Environmental Effects Research Laboratory (NHEERL) and the National Exposure Research Laboratory (NERL), which can conduct experiments and supply data for analysis and modeling by NCCT scientists. The Center is tied into a number of the research activities in these laboratories, including the Endocrine Disrupting Chemicals, Drinking Water, Safe Pesticides/Safe Products, and Human Health Research Programs. NCCT has allocated a fraction of its resources toward the achievement of goals within those ORD programs.

NCCT also has developed three Communities of Practice (CoP) in chemi-informatics, biological modeling, and categorization and prioritization. The purpose of the CoPs is to unite scientists

who have a common interest in an area in which NCCT is a center of excellence. The CoPs are becoming a means of coordinating activity and communicating progress on an informal, grass-roots level. Outreach also has taken place to program offices within EPA, especially the Office of Pesticide Programs. This office is supplying data that are being used as part of the ToxCast project, and is likely to be an early adopter of the predictive and priority-setting tools being developed by the Center.

NCCT is doing a good job of joining forces with others outside the Agency, particularly at NIEHS. The arm of the National Toxicology Program that operates at NIEHS has a strong interest in high-throughput methods for predicting toxicity, a project that is complementary to activity at the Center. NCCT and NIEHS have done a good job of information sharing and have developed a constructive working partnership in which data and analysis methods will be shared. NCCT also is establishing collaborations internationally, coordinated through the Organization for Economic Co-operation and Development (OECD). OECD's project entitled "Molecular Screening for Characterizing Individual Chemicals and Chemical Categories" has similar goals as the ToxCast project. OECD has recognized that ToxCast can serve as a foundation for its project and is developing an international consortium that will build on ToxCast. It is likely that a number of nations and private companies will join this consortium in the coming year. Furthermore, the recent MOU among NCCT, NIEHS, and NHGRI promises to be the most important and extensive collaboration yet for ToxCast and NCCT. In summary, NCCT is doing an excellent job at outreach, which in turn is enhancing its ability to fulfill its mission.

In conclusion, the BOSC Computational Toxicology Subcommittee believes that NCCT is making exceptional progress toward its mission. We are pleased to provide advice on this important Center and look forward to future opportunities to provide timely advice to guide and improve NCCT and its programs.

Sincerely,

Gary S. Sayler, Ph.D.
Chair, BOSC