Appendix

Additional responses and updates on specific issues and questions posed in Dr. Shubat's letter dated December 21, 2011. Many of these will benefit from further discussion over time.

- ***General Issue: CHPAC emphasized the importance of synthesizing and communicating research accomplishments, their usefulness, and their impact to a variety of different audiences (research translation).***

  ORD response: Within the EPA, each ORD program has regular meetings with Program Office and Regional partners to develop common program goals, report findings and prioritize new directions. Continual communication with our partners is critical to the utility of the research products and their impact on policy decisions and ultimately, the protection of public health. Specific to children's health, ORD has established a cross-program Children's Health Work Group to foster coordination of research relevant to children's health. This group includes the Office of Children's Health Protection (OCHP) and other EPA partner participation in developing an integrated roadmap of children's health research across ORD. We envision this roadmap to include an interactive visual framework with links to various program components where more detailed information and points of contact for each research component can be found. We also see value in building a children's environment health protection "community of practice" to connect researchers working on children's health issues both inside and outside the EPA. ORD's open approach to planning and implementing research includes review of all research programs by ORD's Board of Scientific Councilors and input from our Science Advisory Board as well as CHPAC. Our goal is to harness creative thinking by the research and public health communities to advance knowledge about children's health and chemical safety and apply it broadly to further children's health protection and promotion.

  To make information available to the public in appropriate forms, we are translating our research products into synthesis papers, fact sheets and multi-media "science notebooks" that convey complex information in clear and public-friendly ways. We are also developing web-based tools to enable public access to a wide variety of information. For example, efforts are underway to link age-specific exposure factor data to databases and tools used by local governments and public health authorities, health care providers and parent/educational advocacy groups. We hope to provide highlights of ORD research and activities to OCHP for inclusion in their regular list-serve communications which reach a broad readership that includes EPA regional scientists, school coordinators, and pediatricians involved in the EPA-Agency for Toxics Release and Disease Registry (ATSDR) Pediatric Specialty Units in each EPA Region.

  Finally, we recognize the importance of communication and translation across the federal government. For example, as a result of regular meetings with NIEHS on the EPA-NIEHS Children's Centers program, a new factsheet that features descriptions of each active Center is posted prominently under children's health on both the NIEHS and EPA websites (http://www.epa.gov/ncer/childrenscenters/). This web site also includes links to currently funded centers and final reports from others, and to a concise public-friendly synthesis of accomplishments of the first ten years of the Centers Program (1998-2007). Most recently ORD's National Center for Environmental Research (NCER) has launched a monthly webinar series about the Children's Centers, featuring Center directors and Principal Investigators http://www.epa.gov/ncer/events/index.html#febcehc-webinar. This series is being advertised widely within and outside the Agency and NIEHS. NIEHS is hosting the annual Children's Centers' grantee

meeting (open to the public, March 6-7, 2012) at the National Institute of Health (NIH) Natcher Center where a large audience can be accommodated. Finally, ORD is actively engaged with the Federal Taskforce on Children's Health Protection (for which Peter Grevatt, OCHP is the lead for the EPA) to define how the EPA can best contribute to national and international efforts.

- ***General issue: CHPAC emphasized the importance of having metrics by which to measure whether we are reaching our sustainability and health protection/promotion goals.***

  ORD response: Sustainability metrics are considered essential for ORD to measure the effectiveness of our research programs. Across ORD, each program has specific tasks to develop and validate sustainability metrics, and these are being built into Agency performance measures related to the EPA Strategic Plan. These include developing and improving indicators of children's health that can facilitate public health tracking for childhood diseases and conditions. We expect this indicators research to contribute to the EPA's *America's Children and the Environment Report* and the EPA's *Report on the Environment*. The Air Climate and Energy Research Program (ACE), CSS and SHC have initiated collaborative efforts with CDC in this regard and are working with community leaders and decision-makers to test the usefulness of new public health and sustainability metrics gathered at community and regional scales. We recognize the need for metrics specific to children and their age-specific health conditions, developmental stages and vulnerabilities. Thus, we concur that meaningful metrics are essential for measuring the effectiveness of the EPA's policies, and for justifying their costs and evaluating their benefits to the community with respect to economic, health and ecological considerations.

- **Chemical Safety for Sustainability Program (CSS)**

  CHPAC commented: *At the July meeting, an ORD spokesperson for the Chemical Safety for Sustainability Research Program (CSS) described program realignments that result in new research topic areas, such as inherency, systems modeling, and life cycle considerations. The CSS framework contains much more detail on strategies for sustainability, and the CSS research action plan provides information useful to CHPAC members interested in knowing how children's environmental health research will be advanced through the realignment.*

  By focusing on the populations and life stages most susceptible to harm, the health of the general population may be protected and promoted. This may mean putting a high priority on determining, for any particular chemical, whether hazards to early life stages have been appropriately and adequately evaluated. While great strides have been made over the past twenty years to ensure that life stage appropriate studies are conducted, most toxicological studies that are being used to develop regulatory standards and assess chemical safety were conducted using mature animals. While theses historical data are valuable, new studies must be designed to assess potential effects on prenatal and early life stages.

  High throughput testing, which has been promoted as a method to rapidly build a new data base related to inherent chemical properties and cellular and molecular changes in response to a chemical, falls within the scope of the CSS research action plan. This new method of toxicity testing is expected to generate a large amount of data on early cellular and molecular changes that are predictive of adverse effects on human health and development. Several CHPAC members have expressed concerns that the potential for in vitro *testing to predict chemical effects on embryogenesis, neurodevelopment, endocrine and immune function during early childhood is poorly understood at this time.*

ORD response: In the traditional testing paradigm, most data on developmental exposure(s) come from studies that require large numbers of pregnant animals and their offspring. These studies are too slow and costly to meet the efficiency needed to address the potential risks of thousands of new and existing chemicals for which data are needed. The EPA and others in the research community are continually working to improve our testing for developmental and other toxicants. We are striving to increase the power of tests to detect effects while reducing the number of animals used. In addition, we are seeking greater understanding of how chemicals perturb development in humans with less reliance on extrapolation from animal models. Technical and biomedical achievements in recent years have produced newer, more efficient, *in vitro* technologies that can be run quickly on large numbers of chemicals and can provide mechanistic information, with less reliance on animal usage.

The challenges in utilizing this information for a chemical management program are significant, not least of which is the difficulty of recapitulating *in vitro* the complexity of a biological system during its development and interactions with maternal and childhood factors.

CSS is geared to meet this challenge. It brings together researchers with broad technical expertise in exposure modeling, systems biology, computer sciences, and computational toxicology. Much of the work to advance understanding of how chemicals interact with important biological processes inside the embryo, pregnant mother, or developing child is described in CSS *Systems Models*. This research theme aims to generate, utilize, and integrate chemical, biological, and toxicological information at various levels of biological organization (e.g., molecule, cell, organ, and organism), such that the potential toxicity of a chemical can be evaluated with enhanced predictive power. Using innovative technologies such as automated high-throughput screening (HTS), informative data on the biological effects of a large number of chemicals and their associated adverse outcome pathways (AOPs) are being compiled. These groundbreaking approaches have quickly produced results that are being used to help prioritize chemicals for further testing and to help build "virtual tissue" models capable of integrating and encoding data from many sources, informing potential effects of developmental exposure(s) during prenatal and early life stages.

Production of tools for evaluating cross-species conservation of molecular targets and/or key events is a means to predict the relative sensitivity or susceptibility to chemical exposure(s). Outcomes from CSS *Systems Models* research will synergize with CSS *Biomarkers,* guiding researchers toward diagnostic biomarkers that are relevant to developmental exposure(s) or indicative of key events for AOPs associated with embryogenesis, neurodevelopment, endocrine, and immune function. This synergism can promote a more effective utilization of public biomonitoring data (e.g. NHANES) to inform which compounds are of concern and metrics to follow for evaluations (e.g., reductions in levels of lead and perfluorinated chemicals in blood) and improved methodologies for early lifestage-specific risk assessment (e.g., problem scoping and analysis). It can also guide experimental designs in SHC's *Enhancing Children's Health* project that aim to characterize *in utero* factors (e.g., chemicals, diet, stress) influencing developmental health and disease in susceptible life stages and groups, and in community settings.

CHPAC commented: *Members present at the July meeting raised the following points related to this research strategy*:

1. *ToxCast seems to be intended as a predictive model as opposed to being part of a tiered system of testing. There is a concern that if ToxCast rules out chemicals for further testing, biological effects relevant to early life stages could be missed.*

ORD response: ToxCast was initially designed as an HTS chemical prioritization research program. It is well underway toward providing information on 1060 chemicals across ~600 assays. A new implementation of ToxCast known as the "EDSP21 Work Plan" was developed by OSCP/OCSPP with input from ORD scientists (http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf). "EDSP21" describes an approach for using computational *in silico* models and molecular-based *in vitro* HTS assays to prioritize and screen chemicals to determine their potential to interact with the estrogen, androgen or thyroid hormonal systems and steroidogenesis (EATS). This is part of a multi-year transition of the Endocrine Disruptor Screening Program (EDSP) to validate and more efficiently use computational toxicology methods and HTS. This would enable the Agency to more quickly and cost-effectively assess potential chemical toxicity. The EPA also intends to prioritize industrial chemicals for review and possible action under the Toxic Substances Control Act (TSCA). For example, ToxCast HTS data tools could be used to prioritize a chemical for review or targeted testing based on qualified predictive models for reproductive or developmental toxicity.

2. *Assurance that adverse effects relevant to early life are captured by testing systems such as ToxCast (or at least not dismissed) is needed. This was expressed as a need to validate the high throughput testing related to biological endpoints relevant to prenatal development and children's health.*

ORD response: Profiling environmental chemicals by biochemical and cellular *in vitro* assays raises important concerns about the means by which this information can be translated into lifestage-specific risk assessment. First-generation (Phase I) ToxCast predictive models have now been published for reproductive toxicity [Martin et al. 2011] and developmental toxicity [Sipes et al. 2011]. These models anchored *in vitro* data to *in vivo* endpoints for a set of ~300 data-rich chemicals. Pathways for endocrine disruption [Reif et al. 2010], embryonic stem cell differentiation [Chandler et al. 2011] and disruption of blood vessel development [Kleinstreuer et al. 2011] have been linked to the Phase I ToxCast *in vitro* data. For the next ~700 compounds in Phase II, where animal toxicology is less well-characterized, CSS will develop plausible model structures that deal with the possibility of additional relevant interactions and components beyond those represented in the first-generation predictive models. Fact sheets on these ToxCast models are available from the ORD/NCCT homepage: http://www.epa.gov/ncct/download_files/factsheets/ToxCast%20Models%20Fact%20Sheet-Nov%2010%202011.pdf.

A longer-term challenge is to extend these predictive models into what we call dynamic multi-scale simulations of developing tissues and physiological processes. These simulations can, in a sense, be viewed as a translation of statistically meaningful (mathematical) relationships into biological context. The computer simulations use information from various databases and attempt to reconstruct, in a visually simple way, the development of embryonic structures such as a limb-bud or blood vessels. The user can then add a stressor such as a chemical exposure and watch as the computer predicts and shows with computer generated graphics how that chemical could change development. CSS *Systems Models* is tasked with the design, development and implementation of such virtual tissue models for the liver, embryo, and endocrine system. For example, sophisticated computer models of embryonic blood vessel development in the Virtual Embryo task (CSS

2.2.2) or interactions between hypothalamic-pituitary-testis in the Virtual Endocrine task (CSS 2.2.3) are built from vast scientific knowledge of complex biological systems. These models can potentially be used in toxicological assessments relevant to children's health by simulating what might happen when the mother or child is exposed to different chemical exposure scenarios.

Challenges for virtual tissue science and technology development are being facilitated by academic collaborations through the EPA's STAR program, such as the Texas-Indiana Virtual STAR Center (TIVS), which is devising strategies to reconstruct detailed *in silico* models of complex developmental processes and toxicities. ORD/NCER is also in the process of awarding 8 additional grants that will probe toxicity pathways of concern for developmental toxicity, with the goal of moving these into HTS assays to broaden our coverage of biological space.

3. *The similarities between high throughput screening for toxicity and testing that result in screening out pharmaceutical chemicals were described. However, there is a fundamental difference in the result of a pharmaceutical company's rejection of a chemical for further development and developing a full understanding of what is "safe" for human exposure. Many, many tiers of additional pharmaceutical testing and use trials are necessary to demonstrate both efficacy and a lack of toxicity, while the current vision for Tox21 is additional tiers of testing to demonstrate toxicity rather than safety.*

ORD response: CSS recognizes that 'drug discovery and attrition' is geared toward the efficacy of the product and is intolerant of false positives (for reasons of time and money invested), whereas 'chemical risk management' is intolerant of false negatives (to avoid missing potential health risks). The testing strategy adopted in ToxCast Phase I has proven to be conservative overall (false positives >> false negatives) with good to excellent balanced accuracy (70-80%). Currently, we are prospectively evaluating the predictiveness of these models through Phase II of ToxCast. An important CSS concept is the integration of large amounts of screening-level data with additional tiers of toxicity information. Program-specific CSS "*Dashboards*" are web-accessible, customized graphical user interfaces that link and translate information and knowledge to regulatory decision-makers. Using customized dashboards, stakeholders can seamlessly access summary information derived from data, publications, decision-rules, predictive models, and so forth. Through CSS, 'Lifestage-specific dashboards' could, for example, be developed in collaboration with OCHP to provide access to information and models relevant to embryogenesis, neurodevelopment, endocrine, and immune function.

4. *Some CHPAC members expressed concern that ToxCast is reductionist. While the conceptual approach for mixtures and multiple chemicals is understandable and laudable, there is a basic concern that focusing on what might be relatively few changes in protein expression or genomic change may not capture the potential range of interactions in the human body.*

ORD response: ToxCast probes the fundamental nature of chemical interaction(s) with their potential molecular targets and cellular consequences. Importantly, this covers a broad range of concentrations. As such, dose-response relationships can be directly evaluated across literally hundreds of assays. CSS recognizes that toxicity is an expression of the propagation of lesions into more complex tissues and that cellular interactions, such as between immune cells and endothelial cells during angiogenesis for example, play important roles in utero-placental development,

embryogenesis, and other AOPs linked to childhood development. CSS also recognizes the need for predictive hierarchical models spanning several scales from molecular networks to tissue- and organism-level phenotypes. For example, the Virtual Embryo task integrates multi-dimensional data with vast biological knowledge and translates this information into multi-scale, multi-cellular models that can simulate outcomes following specific chemical perturbations. Whereas ToxCast provides the infrastructure to predict pathways of toxicity, virtual tissue models may translate these predictions into simulations that reconstruct the potential range of interactions inside the embryo, fetus, infant or child.

As ORD's computational toolbox continues to evolve, we see the inclusion of additional lifestage related effects to the broader context of developmental programming (functional deficits, latent manifestations); this will move the science beyond severe outcomes (low birth weight, malformations). As we come to better understand AOPs, and how these pathways interact with each other, our virtual tissue models will be able to perform "what if" questions about exposures to multiple chemicals. This will someday allow us to flag combinations that pose the highest levels of hazard.

5. *EPA seems to have assumed the burden of proof of sustainability and safety in the CSS research strategy. The contribution of industry is not apparent.*

ORD response: The Toxic Substance Control Act (TSCA) puts the burden of proof on the EPA. CSS research will support the Office of Chemical Safety and Pollution Prevention (OCSPP) in its mission by developing better chemical prioritizing and testing methods for use by the Agency and industry. In addition, partnerships with industry, such as voluntary actions to reduce/prevent pollution are often motivated and informed by CSS research.

Industry also contributes to CSS research through Material Transfer Agreements (MTA) between ToxCast and industry partners. In some cases, the MTA partnership entailed a donation of 'failed drugs' to Phase II. Other cases entailed pilot studies to qualify predictive toxicology of ToxCast signatures or virtual tissue simulations for developmental effects. The ExpoCast program in CSS *Systems Models* has catalyzed a limited research initiative by industry to support development of exposure models and metrics for improved exposure-based chemical prioritization. ORD/NRMRL has a number of industry partnerships relevant to the CSS *Life Cycles* research theme.

ORD welcomes the opportunity to work with industry, especially in the alignment of a research strategy toward capturing and validating early life endpoints in high throughput testing approaches and developing metrics that can be applied by external organizations to improve the sustainability of their products. The ORD HTS program is one key tool in this effort.

CHPAC commented: *CHPAC members received an acknowledgement from ORD that the EPA sees the issue of capturing and validating early life endpoints in high throughput testing as a concern. ORD described the new high-throughput assays as one guide to decision-making and explained that the current focus is on developing priorities for further testing. CHPAC members are pleased that Office of Children's Health Protection (OCHP) staff are providing input to EPA programs conducting computational toxicology work (for example, the virtual embryo project) so that early life stages and developmental windows of vulnerability are comprehensively considered in the research.*

ORD response: Cross-training has been ongoing in CSS between OCHP and the CSS Virtual Embryo team. ORD welcomes the chance to work with CHPAC and would be interested in a new 'Children's Health Community-of-Practice in Children's Health' (CH-COP), similar to one hosted by CSS in computational toxicology [http://www.epa.gov/ncct/communities_of_practice.html]. The purpose of the CompTox COP is to provide regular updates to stakeholders interested in research progress. It serves as an effective forum for discussing plans for the advancement and utilization of exposure science and computational toxicology to address the EPA's needs for chemical screening, prioritization and toxicity testing. The CompTox COP is composed of more than 300 people who have an interest in encouraging computational toxicology usage and exposure science in helping to implement the EPA's mission of protecting human health and the environment. Anyone can join the COP and members include staff from the EPA, other federal agencies, industry, academic institutions, professional societies, nongovernmental organizations, environmental non-profit groups, state environmental agencies and more. We would be pleased to add interested members of CHPAC to the stakeholder database. You will then receive updates about the Communities of Practice and announcements about research progress.

A focused CH-COP could serve as a focal point for cross-training activities and could open the door to further discussion between ORD, OCHP, CHPAC, and the broader community. CH-COP would foster the shared vision across diverse communities focusing on public health, toxicology, basic science, and technology development. For example, cross-training can delve into why a pathway-based risk assessment is needed and the problem being addressed; how we are addressing the problem using contemporary developmental biology; and how a systems-based approach can be used in a new risk assessment paradigm (e.g., CSS is developing *NextGen Risk Assessment* case studies for phthalates).

CHPAC commented: *CHPAC would like to hear more explicitly what health effects related to early life stage exposure and development (including prenatal and preconception exposure and development) will be incorporated into high throughput screening (e.g., assay selection for neurodevelopmental toxicity) and if specific health endpoint correlates are not included, what additional testing would be required before screening out a chemical for further research.*

ORD response: Much of the data generation in the research program relevant to developmental processes and toxicities will come from assays residing in CSS *Systems Models*. For example, HTS data is being collected on a variety of assay platforms designed to identify a range of pathways that contribute to normal embryo and fetal development, and for which alterations in the pathway are predicted to result in both specific and general development deficits from early embryo and fetal loss, to birth defects, to health conditions related to abnormal hormone signaling, defects in organ formation as may be secondary to inadequate blood supply during development, and behavioral deficits due to altered development of the brain and nervous system. Accordingly, exploratory platforms include mouse embryonic stem cell differentiation; human pluripotent stem cells (derived from adult tissues); neural cell differentiation and neural crest biomarkers from neuronal cell lines; vasculogenesis/angiogenesis assays for blood vessel formation and growth; zebrafish embryogenesis for early steps in embryo development; and cell lines relevant to studies on the hypothalamic-pituitary-gonadal and thyroid-brain axes. Specific health endpoints are represented in a computable manner in the ToxRefDB database [http://actor.epa.gov/toxrefdb/faces/Home.jsp]. ToxRefDB includes over 30-years of registrant-submitted animal studies worth >$2-billion for chronic/cancer in two-year bioassays in rats and mice; multigeneration reproductive toxicity in rats; and prenatal developmental toxicity in pregnant rats and pregnant rabbits. It has been expanded recently to include data on developmental neurotoxicity in rats and may in the future include data on

developmental immunotoxicity. ToxRefDB provides a resource to anchor the newer pathway-based paradigm, in which toxicity is predicted from *in vitro* signatures, to a more traditional outcomes-based paradigm that focuses on observational endpoints. ORD can provide details and progress to CHPAC during regular meetings, CH-COP webinars, and scientific publications.

CHPAC commented: *ORD suggested that with the possibility of conducting 8,000 simultaneous assays EPA anticipates a more comprehensive understanding of mixtures will emerge. CHPAC would like to hear explicitly how a systematic study of the cumulative effect of mixtures will be conducted in ways that can be correlated with whole animal studies. In addition, CHPAC would like to hear about both plans and outcomes for incorporating metabolic activation into high throughput research.*

ORD response: The aim of CSS *Cumulative Risk* research is to identify, predict, and assess the potential human health and environmental outcomes that may occur due to multiple and continuous exposures to chemicals, with a focus on those chemicals found in consumer products. We would welcome the chance to convey our progress to CHPAC on the following topics in more detail. For example, researchers are assessing the cumulative risk of perfluorinated chemicals (PFCs) that have been tested in ToxCast. HTS datasets can now be mined for molecular targets or pathways potentially affected by PFCs. Virtual tissue models can be used to generate 'mixed effects models' for specific developmental processes (e.g., angiogenesis) and the models can be qualified against empirical data from targeted experiments or a high throughput mixtures study.

Methods are also being developed to identify testing priorities based on potential for children's exposure to chemical mixtures in their home environment, for potential follow-on work in the CSS *Cumulative Risk* [Tornero-Velez et al. 2011].

In terms of incorporating metabolic activation into high-throughput research, CSS *Extrapolation* and *Systems Models* projects are utilizing physiologically-based dose response (PBPK) models to integrate exposure with internal dose; reverse-PBPK models to compare the oral equivalent doses with human exposure estimates from the *in vitro* data; and virtual tissue models for cell-level microdosimetry and transport. The latter is considered in detail for hepatic microdosimetry in the Virtual Liver task in metabolically-competent HepRG cells, and for pregnancy (transplacental) and infantile (translactational) exposures in the Virtual Embryo task. Continued refinement of the *in vitro* assays to better reflect *in vivo* adverse effects and special considerations for developmental exposure(s) will eventually allow us to move beyond hazard-based prioritization to early lifestage specific risk assessment.

CHPAC commented: *ORD is working on validation for testing that considers correlations, confounders, and dependent and independent variables for specific types of studies and assays. CHPAC will be a much more enthusiastic advocate of ToxCast and Tox21 testing once the potential for the new testing strategies to predict effects on growth, development, and function have been proven. CHPAC would like to see validation studies such as the recently published EPA computational toxicity research project on prenatal developmental toxicity"' CHPAC would like to hear more about plans for validating the relationship between* in vitro *and* in vivo *toxicity endpoints and see the results of this validation work.*

ORD response: Again, ORD welcomes additional engagement with CHPAC on matters of critical importance to prenatal exposures and early lifestage research. Below is a selection of 2010-2012 publications regarding first-generation predictive models utilizing ToxCast HTS data to

acknowledge the strong activity toward use of the new testing strategy in issues relevant to children's health protection. ORD would be happy to offer fact sheets and presentations to CHPAC on these various topics.

Cohen Hubal E.A., Richard A.M., Shah I.A., Gallagher J., Kavlock R.J., Blancato J.N., and Edwards S.W. (2010) Exposure science and the US EPA National Center for Computational Toxicology. J Expo Sci Environ Epidemiol 20: 231-236

Reif D., Martin M.T., Tan S., Houck K.A., Judson R., Richard A.M., Knudsen T.B., Dix D.J. and Kavlock R.J. (2010) Endocrine profiling and prioritization of environmental chemicals using ToxCast data. Environ Hlth Persp 118, 2-8

Rotroff D.M., Wetmore B.A., Dix D.J., Ferguson S.S., Clewell H.J., Houck K.A., LeCluyse E.L., Andersen M.E., Judson R., Smith C.M., Sochaski M.A., Kavlock R.J., Boellmann F., Martin M.T., Reif D., Wambaugh J.F. and Thomas R.S. (2010) Incorporating human dosimetry and exposure into high-throughput *in vitro* toxicity screening . Toxicol Sci 117, 348-358

Sipes N.S., Martin M.T., Reif D.M., Kleinstreuer N.C., Judson R.S., Singh A.V., Chandler K.J., Dix D.J., Kavlock R.J. and Knudsen T.B. (2011) Predictive models of prenatal developmental toxicity from ToxCast high-throughput screening data. Toxicol Sci 124, 109-127

Martin M.T., Knudsen T.B., Reif D.M., Houck K.A., Judson R.S., Kavlock R.J. and Dix D.J. (2011) Predictive model of rat reproductive toxicity from ToxCast high throughput screening. Biol Reprod 85, 327-339

Chandler K.J., Barrier M., Jeffay S., Nichols H.P., Kleinstreuer N.C., Singh A.V., Reif D.M., Sipes N.S., Judson R.S., Dix D.J., Kavlock R.J., Hunter E.S. III and Knudsen T.B. (2011) Evaluation of 309 environmental chemicals using a mouse embryonic stem cell adherent cell differentiation and cytotoxicity assay. PLOS One 6(6), p. e18540

Sipes N.S., Padilla S. and Knudsen T.B. (2011) Zebrafish, as an integrative model for twenty-first century toxicity testing. Birth Defects Res C 93, 256-267

Kleinstreuer N.C., Judson R.S., Reif D.M., Sipes N.S., Singh A.V., Chandler K.J., DeWoskin R., Dix D.J., Kavlock R.J. and Knudsen T.B. (2011) Environmental impact on vascular development predicted by high throughput screening. Environ Health Perspect 119, 1596-1603

Kleinstreuer N.C., Smith A.M., West P.R., Conard K., Fontaine B., Weir-Hauptman A.M., Palmer J., Knudsen T.B., Dix D.J., Donley E.L. and Cezar G.G. (2011) Identifying developmental toxicity pathways for a subset of ToxCast chemicals using human embryonic stem cells and metabolomics. Toxicol Appl Pharmacol 257, 111-121

Padilla S., Corum D., Padnos B., Hunter D.L., Beam A., Houck K.A., Sipes N., Kleinstreuer N., Knudsen T., Dix D.J. and Reif D.M. (2012). Zebrafish Developmental Screening of the ToxCast Phase I Chemical Library. Reprod Toxicol (in press), doi:10.1016/j.reprotox.2011.10.18

Tornero-Velez R., Egeghy P. and Cohen Hubal E.A. (2011). Application of biogeographical methods to chemical co-occurrence data to identify priorities for mixture research. Risk Analysis doi:10.1111/j.1539-6924.2011.01658.x

Joubert B.R., Reif D., Edwards S., Leiner K.A., Hudgens E., Egeghy P., Gallagher J. and Cohen Hubal E. (2011) Evaluation of genetic susceptibility to childhood allergy and asthma in an African American urban population. BMC Medical Genetics 12: 25. http://www.biomedcentral.com/1471-2350/12/25

Gallagher J.E., Hudgens E.E., Williams A.H., Inmon J., Rhoney S., Andrews G., Reif D.M., Heidenfelder B.L., Neas L.M., Williams R., Johnson M.M., Ozkaynak H., Edwards S.W. and Cohen Hubal E.A. (2011) Mechanistic Indicators of Childhood Asthma (MICA) Study: piloting an integrative design for evaluating environmental health. BMC Public Health 11: 344. doi:10.1186/1471-2458-11-344

Egeghy P.P., Cohen Hubal E.A., Tulve N., Melnyk L., Morgan M., Fortmann R. and Sheldon L. (2011) Review of Pesticide Urinary Biomarker Measurements from Selected US EPA Children's Observational Exposure Studies. Int. J. Environ. Res. Public Health 8(5), 1727-1754

Knudsen T.B. and Kleinstreuer N.C. (2012) Disruption of embryonic vascular development in predictive toxicology. Birth Defects Res C 93, 312-323

Judson R.S., Mortensen H.M., Shah I., Knudsen T.B. and Elloumi F. (2012) Using pathway modules as targets for assay development in xenobiotic screening. Mol BioSyst 8, 531-542

Wetmore B.A., Wambaugh J.F., Ferguson S.S., Sochaski M.A., Rotroff D.M., Freeman K., Clewell H.J. III, Dix D.J., Andersen M.E., Houck K.A., Allen B., Judson R.S., Singh R., Kavlock R.J., Richard A.M. and Thomas R.S. (2012) Integration of dosimetry, exposure and high-throughput screening data in chemical toxicity assessment. Toxicol Sci 125: 157-174

CHPAC commented: *CHPAC is concerned about translating this research, specifically in 1) explaining the complexity of this work to scientists, medical professionals, and community members; and 2) using this work to protect children by developing appropriate interventions based on this work and measuring the success of such interventions. CHPAC would like to hear ORO plans for sharing and using the results of the CSS work.*

ORD response: The ORD research programs are in the process of developing a communications strategy to guide how research will be shared with external audiences. The purpose of the communications strategy will be to increase audiences' awareness, interest and usage of ORD research. The communications strategy will include goals, objectives, target audiences, communication strategies and a timeline. As mentioned already, we are developing cross-training programs with OCHP and different levels of outreach to the public and children's centers. Public communities of practice were described above. Fact sheets are developed on a continuous basis, and ORD would be pleased to provide copies of relevant fact sheets as they are generated.

- **Sustainable and Healthy Communities Research Program (SHC)**

CHPAC commented: *An ORD spokesperson discussed how the Sustainable and Healthy Communities Research Program (SHC) integrates multiple programs throughout ORD to work*

toward sustainable and healthy communities. This new strategy comprises aspects of the human health research program, land program (Superfund), and the ecosystems services program. Major SHC themes that relate to children's health research are related to tools and data collection, partner needs, and communities (such as children's settings and built environment factors). ORD described the SHC Children's Health Project, which has three tasks: 1) children's exposure factors (including a study of determinants of exposure to chemicals in the environment for early life stages); 2) health effects from early life exposures (and the latent or chronic effects resulting from early life exposures); and 3) systems approach to community-based children's health.

Members at the July meeting and subsequent discussions raised the following points related to this research strategy:

1. *CHPAC members suggest that the social determinants of health model is a useful way to address multiple critical factors (such as economic disparities and environmental justice).*
2. *CHPAC did not hear a strong theme of addressing or acknowledging issues surrounding environmental justice.*
3. *CHPAC expressed concern that EPA may not have sufficient staff with the appropriate training and expertise (such as social scientists) for working with communities and their needs.*

ORD Response, items 1-3:
SHC is conducting research about social determinants of health in two projects which were not covered in depth at the CHPAC meeting last July. In the SHC StRAP a topic area called "*Improving Human Health and Well-being for Community Sustainability*" includes projects on "Securing and Sustaining Environmental Justice (EJ)," and "Enhancing Community Public Health," along with the project on "Enhancing Children's Health."

The EJ project consists of a series of tasks designed to address the goals of the EPA's Plan EJ 2014 (http://www.epa.gov/compliance/ej/resources/policy/plan-ej-2014/plan-ej-2011-09.pdf). Scientists from SHC and OEJ will be describing this research in more detail at the upcoming CHPAC meeting this spring. Briefly, this project includes:

- Research on the fundamental determinants of environmental inequity (conducted by grantees in Centers of Excellence in Environmental and Health Disparities developed in collaboration with NIMHD);
- STAR research examining how social and economic factors can exacerbate the impacts of environmental chemical exposures and methods for evaluating this complexity using multi-factorial approaches;
- Development and application of tools communities can use to evaluate their specific problems, identify inequities and their causes, and weigh the costs and benefits of proposed solutions;
- Development of guidance for the EPA to use in order to better evaluate the impact of its policies and actions with respect to potential environmental inequities;
- Capacity building activities and training for ORD staff in the area of EJ and for communities in how to work with governmental and other groups toward common goals.

The Public Health project also considers social determinates in its plans to:

- Identify and characterize key public health conditions and their causes relative to the environment (e.g. asthma);
- Develop and verify public health indicators that can be used to track the benefits and effectiveness of risk management actions (working with CDC);

- Develop and apply (in case studies collaboratively with at risk communities) tools for community public health assessment and remediation (including Tribal science grants).

Consideration of environmental equity and children's unique vulnerabilities is inherent in all this research, and in other ORD programs. The EPA is working to leverage our existing resources in the social sciences. Current and new STAR grants in the EJ and Community Public Health tasks will add much needed social science expertise in the near term as ORD takes steps to increase its in-house capacity. ORD's Science Advisory Board has made this recommendation as well.

4. *Members encouraged EPA to partner with groups that focus on learning environments across the childhood and adolescence trajectory, including child care and schools, and suggested that EPA determine the types of community capacity building that are successful and build on that knowledgebase.*

ORD response: New research is being solicited in FY12 as STAR grants and as a new "formative" center in the Children's Center Program to address child care environments and school environments/school buildings. This is a proposed topic for future CHPAC discussions. Input on writing teams for these RFAs was provided by OCHP, Office of Air and Radiation, and the Regional children's health coordinators to help respondents understand how research can help inform Agency policies and guidance in these settings across the childhood and adolescence trajectory.

5. *It was not clear to members that EPA consistently includes preconception and prenatal life stages in strategies aimed at children's health.*

ORD response: The EPA has long considered preconception and prenatal exposures essential considerations for risk assessment as articulated in its Guidelines for Reproductive Risk Assessment Guidelines, 1996 (www.epa.gov/raf/publications/pdfs/REPRO51.PDF), Guidelines for Developmental Toxicity Risk Assessment, 1991 (http://www.epa.gov/raf/publications/pdfs/DEVTOX.PDF) and Cancer Guidelines and supplemental guidance (http://www.epa.gov/cancerguidelines/ and http://www.epa.gov/cancerguidelines/guidelines-carcinogen-supplement.htm). These guidelines are integral to considerations in human health assessments in the HHRA program including IRIS, provisional peer reviewed toxicity values (PPRTVs), and integrated science assessments (ISAs).

ORD recognizes the growing concern that chemical exposures, nutrition and other factors may operate through epigenetic mechanisms to alter the programming of gamete and embryo development with potential new implications for children's health. Prenatal development is an area of major focus in CSS's Virtual Embryo project described earlier. SHC's Children's Health project includes a task developing and using animal models to evaluate the impact of early exposures on later health impacts. In addition, many STAR grantees in the Children's Centers Program are evaluating levels of priority chemicals in pregnant women and potential health impacts and body burdens in children born to these women. ORD's commitment to the Children's Centers Program over the last 14 years has fostered ground-breaking research using this longitudinal approach in defined cohorts. Information gained from these studies as well as lessons learned with respect to study design and exposure metrics will not only be valuable to the EPA but also to the National Children's Study (NCS) funded by NIH (www.nationalchildrensstudy.gov). A STAR grantee meeting in March 2012 will report results of research focused on early indicators of childhood disease; this workshop is being held on the NIH campus so that staff from the NCS can attend.

Consideration of maternal health and nutrition in all these studies provides insights into the importance of preconception health.

6. *Members commented that it is important for EPA to sustain capacity building programs and that EPA should identify resources to sustain community efforts to improve environmental health.*

ORD response: Resources are being prioritized to insure that progress can be made in capacity building for EJ and for participatory research with communities. Pilot studies are being conducted to develop and evaluate the usefulness of tools for improving environmental health in community and tribal settings and in collaboration with community members as well as State, Tribal and local decision-makers. We expect to report significant progress on these objectives over the next five years.

7. *CHPAC members noted that it is important to ensure that the community groups asked to participate in research programs and projects are actually part of the community, and suggested that existing community organizations provide excellent communication linkages to the community.*

ORD response: This is a central premise of community-based, participatory research, and a key element of ORD's "path forward" operating principles.

8. *Members also suggest that Children's Environmental Health Centers integrate community participatory research methodology into all research and involve more representatives from the residents of the community they serve in their decision-making around research.*

ORD Response: Previous and current Requests for Applications (RFAs) for the Children's Center Program, developed with NIEHS, specify that all full Centers must have an outreach and/or community participatory research "core." The currently funded Centers are partnering with a variety of groups such as medical providers, educators, and community organizations/parent groups. More information can be found at http://www.epa.gov/ncer/childrenscenters/ and will be provided in the new monthly Children's Centers webinar series mentioned earlier.

9. *Members expressed some reservations about the concept of empowering communities to conduct risk assessments, as experience has shown that communities do not have the resources or expertise to conduct risk assessments, but expect state and federal agencies to provide guidelines and regulations that will ensure the public's safety.*

ORD Response: We did not intend to imply that communities conduct risk assessments in the regulatory sense. State and local governments have decision making authority with respect to enforcing federal regulations, setting policies for land use and zoning, and taking local public actions. The emphasis of the SHC program is to provide improved tools for these local decision makers and provide greater transparency for communities to participate in and contribute their input to the decision making process. SHC is developing tools that will help communities access and synthesize information and data on a wide variety of environmental stressors and use that information to better define their environmental and health problems and options while evaluating the advantages and potential adverse consequences of various decisions (or "alternative futures"). We are working on tools and interactive spatial displays that could be accessed by the public (web-based and user-friendly) and that provide "one stop shopping" for exposure data of various sorts,

ecosystems services data, policies, and other resources. ORD will work with community partners/decision-makers on how to use these tools and continually modify them as needed. The goal is to help community decision-makers make decisions that promote sustainability and health while avoiding unanticipated consequences.

10. **CHPAC commented**: *CHPAC is interested in how social determinants of health can be explicitly, and in a measured way, incorporated into a systems approach to community-based children's health. CHPAC is interested in the EPA's plans to transfer or translate the science to community action. A concern was expressed about the extent to which community and school based interventions have been proven effective (i.e., are proposed interventions grounded in science?). Measures of success are needed in order to determine whether SHC work results in healthier and safer communities. CHPAC would like to hear ORD plans for measuring the progress of the SHC work.*

ORD response: A major goal of SHC is to identify, develop and improve ways to measure and weigh the social determinants of health, including children's health at all developmental stages. In addition to in-house and STAR efforts mentioned above, we expect research funded by new RFAs on childcare and school environments to help address this question. "How do we show that various interventions improve children's health, development and performance?"

- **Human Health Risk Assessment Program (HHRA)**

CHPAC commented: *Human Health Risk Assessment (HHRA) topics described in the ORD power point presentation included themes of dose response assessments (the Integrated Risk Information System); Integrated Science Assessments for criteria air pollutants; community and technical support for exposure and health assessments; and methods, models, and approaches to modernize risk assessment for the 21st Century.*

ORD response: We would like to expand the conversation with CHPAC on HHRA at an upcoming CHPAC meeting where we can clarify the many objectives and activities in HHRA that support modernization of risk assessment.

Suggested topics could include: How will HHRA respond to the recommendations of the "next generation" risk assessment, as conceived in the NAS "Silver Book" *Science and Decisions, Advancing Risk Assessment (2009),* and Phthalates and Cumulative Risk Assessment Task Ahead (2008)?

Members raised the following questions and points related to ORDs research programs:

1. *What are the major research goals, timelines, and outcome measures? What childhood illnesses and developmental problems are being targeted and how are those associated with environmental exposures? What exposures are targeted and what is known about how those affect children's health? How will EPA measure its success or failure? Has past research been successful in reducing illness rates? How do current asthma rates compare with rates 10 and 20 years ago? Blood lead levels are lower, but attention deficit disorders and other learning problems seem to be more common and college entrance test scores are lower. Can the new research program explain these contradictory trends?*

ORD response: ORD will address these questions broadly since they apply across ORD programs. The StRAPs for all our programs and the children's health roadmap will help clarify goals, timelines and outcome measures. Timelines are specific to various projects within the ORD StRAPs, need to be flexible and can change as a result of changing resources. Ongoing engagement with CHPAC will enable ORD to address these questions as research questions are answered and new priorities arise.

Answers to questions about changing trends in such childhood conditions and disease burdens such as asthma prevalence and neurodevelopmental disorders will require combined efforts of HHS as well as the EPA and other public health partners as these are complex societal and health issues. SHC and ACE are actively exploring opportunities for collaborative projects with CDC that would help integrate public health tracking and biomonitoring data into community-based exposure models, tools and public health intervention approaches. We expect that SHC research on public health indicators will contribute to these efforts and also be useful in the conduct of Health Impact Assessments. ORD is an active partner with CDC and other Agencies in a workgroup that recently developed a National Action Plan for Reducing Racial and Ethnic Asthma Disparities (part of the Federal Taskforce on Children's Health Protection and Safety), and is conducting research in support of that action plan, particularly on intervention strategies and asthma causation. This action plan should be publically accessible in the near future. Research related to asthma, lead, and neuro-developmental deficits, being implemented in SHC and ACE, includes both in-house and STAR research in several of the Children's Centers in SHC and Clean Air Centers in ACE. In turn, the HHRA uses data and information derived from ORD and other research to assist the Agency in evaluating risks associated with certain exposures, and thereby supports the regulatory and enforcement roles of the Agency.

2. *Environmental health research is most likely to produce a useful outcome when it targets a specific problem. CHPAC would prefer that EPA focus on improving children's health by identifying and reducing exposure to harmful substances instead of studying the effects of unabated exposures that are known or suspected to be hazardous.*

ORD Response: CSS research helps the Agency identify evaluate and predict the risks of potentially harmful exposures to chemicals and other materials. HHRA helps the Agency understand, evaluate and remediate risks of such exposures. Research in HHRA will contribute to improved risk assessment approaches and guidance for Agency use. Beyond this attempt to clarify the scope of HHRA research distinct from the EPA's overall mission, ORD is happy to engage in dialog with CHPAC to better understand this concern.

3. *CHPAC members have asked if additional children's exposure factors and risk information should be developed. There is concern among CHPAC that allergens and asthma triggers have not been assessed as rigorously as the approach used for chemicals. The Integrated Risk Information System is used for chemicals, not biologicals or pathogens, and work should be conducted to characterize risks from cockroach antigens, molds, harmful algae, and complex mixtures.*

ORD Response: In contrast to specific chemicals of concern, cockroach antigens and molds (and harmful algae) are complex in composition and often undefined. Some research has identified components of these antigenic materials that may be the proximate toxicant/stressor and could be approached in a fashion similar to that for chemical risk assessment. However, these naturally occurring substances are not regulated at present. Rather, guidance developed by EPA Programs for

identifying and removing harmful mold, and for understanding and avoiding asthma triggers is provided to the public on the EPA's website.

The association between cockroach antigens and certain molds and allergies is well-known. Children's Center research has previously demonstrated the health (and economic) benefits of applying "Integrated Pest Management" which includes improved cleaning methods to remove such allergens, as has been used by public housing authorities to protect children's health. Within current budgetary limitations, in-house research is evaluating better methods for identifying specific molds and the extent to which they may cause or exacerbate asthma.
ORD is also interested in the long term impacts of climate and climate change on the types and distribution of aeroallergens including potential for improving public health alerts. STAR grantees funded under ACE are actively investigating the implications of climate change and aeroallergens. Additionally, the National Center for Environmental Assessment provides a recent report on this issue: http://www.epa.gov/ord/gems/scinews_aeroallergens.htm.

4. *The EPA-funded Near Roadways Exposure to Urban Air Pollutants Study (NEXUS), a project of the University of Michigan, demonstrates that near roadway air pollution is a very important metric for exposures to urban pollutants. The relationship between the stage of pregnancy and level of exposure to pollutants is an important aspect of such research.*

ORD Response: Research in several of the Children's Centers is also exploring prenatal air pollution impacts. In addition, the University of Michigan research, which is ongoing in ACE, includes evaluation of a cohort of asthmatic children to better characterize potential near-roadway impacts on existing disease. Further, ORD's NEXUS program in ACE also includes new near-road research in North Carolina.

5. *Questions were raised, as with other research areas, about measuring the result of HHRA utilizing a new research strategy. It was noted that approaches to human health risk assessment will continue to be used (that is, be sustainable) only if found useful. The question was asked how EPA will know that the result of the new strategy is improvements in children's health.*

ORD response: As mentioned at the start, ORD welcomes the opportunity to discuss in more detail the metrics we are planning to develop and use as part of the "NextGen" risk assessment efforts in HHRA and with the EPA's Risk Assessment Forum.

- **Safe and Sustainable Water Resources (SSWR)**

CHPAC commented: *In addition to the three research strategies described above, CHPAC members discussed issues related to Safe and Sustainable Water Resources. Current requirements for tests done on drinking water and air are limited to a relatively small number of chemicals. When an unregulated contaminant is found in a drinking water supply at a level that exceeds the EPA's one-day child health advisory, no action is required to be taken under the Safe Drinking Water Act. A question was raised about whether the Safe and Sustainable Water Resources Research Program will study children's exposure to unregulated contaminants of public drinking water, and if so, members asked what contaminants will be assessed, how many children are exposed, and what is the potential for an adverse health effect?*

ORD response: There are no specific tasks in SSWR that uniquely address issues of children's exposure or potential health consequences to unregulated contaminants in public drinking water. However, SSWR has established linkages with CSS where adverse effects of unregulated drinking water contaminants are being addressed. Two hundred and seventeen compounds on the EPA Office of Water's Chemical Contaminant Lists (CCL1, CCL2, CCL3 and PCCL, http://www.water.epa.gov/scitech/drinkingwater/dws/ccl/) are being evaluated as part of the ToxCast Phase II chemical library. The complete information on the identity of compounds included in this library is available at http://www.epa.gov/ncct/toxcast/files/ToxCast%20Chemical%20Summary%2014Dec2010.pdf

Information on specific assays being used to evaluate the effects of these compounds and the specific assay results is and will be available at: http://www.epa.gov/ncct/toxcast/.

Research to translate specific cellular and molecular effects in the *in vitro* ToxCast assays designed to enhance our understanding the potential impacts of exposure to children will also be addressed in specific research tasks in CSS such as CSS "Systems Models" tasks for data collection and computational modeling for the Virtual Embryo (CSS 2.2.2), which is focused on the predictive toxicology of children's health and development following prenatal or lactational exposure to environmental chemicals.

- **Research partners**

CHPAC commented: *In addition to discussing the individual strategies, CHPAC members expressed interest in the theme of overlapping research communities. Members encouraged EPA to partner with other agencies on research.*

1. *CHPAC members wondered if the CSS research will be limited to currently regulated chemicals and products. An emerging issue of interest to some members is the growing use of nanosilver and other nanomaterials. CHPAC is interested in knowing how EPA will work with other agencies to ensure the safety of these materials. Another group of chemicals of interest are pesticide residues in foods, water, and the indoor environment, which also may require collaboration with offices outside of ORD.*

ORD response: CSS *Systems Models* has a major project focusing on the toxicology of nanomaterials, and a number of nanomaterials are being tested across ~600 assays in ToxCast Phase II. Working with an interagency consortium of 25 agencies, ORD has helped develop the Interagency National Nanotechnology Initiative's Strategic Plan (2011). In turn, the CSS "Nanomaterial-Specific Inherency Issues" project, developed in partnership with OCSPP, is responsive to the needs articulated in this national plan. This close partnership will insure that appropriate research priority is placed on individual chemicals and groups of chemicals of highest importance to the Agency with respect to exposure (including through food) and effects data needs (such as dose response data for limit-setting) to ensure that ORD contributes scientific expertise and data to the timely assessment of risks for regulatory and enforcement actions and reviews of registrations. Also, as part of the Federal Taskforce for Children's Health Protection, ORD is working with OCHP, OCSPP, NIEHS, CPSC and other Agencies to identify chemicals in products that children are most likely to come into contact with in order to develop strategies for avoiding exposures and risks.

2. *It was noted that more research is needed on endocrine disruption, childhood obesity, Type I and Type II diabetes, and developmental disorders including attention deficit and hyperactivity disorders. EPA and Centers for Disease Control and Prevention (CDC) could partner to identify the most prevalent childhood illnesses/disorders that seem to have an environmental component and work together to study causes and design interventions. CDC's Environmental Health Tracking Program and the National Institutes of Health (NIH)/EPA funded Children's Health Study have shared goals of reducing childhood illness and infant mortality and could work closely together.*

ORD response: ORD is working on these important outcomes and towards these necessary ends with CDC, NIEHS and other Agencies. CSS and SHC ("Enhancing Children's Health" project) retain a major emphasis on endocrine disruptors, including their potential long term impacts over the various stages of development and for adult human health. Both CSS and SHC offer expertise to NCS through research and participation on the NCS Interagency Coordinating Committee.

3. *CHPAC encourages ORD to compare research priorities among federal agencies (NIH, CDC, Department of Defense, and Department of Education) and identify potential overlapping research and areas for collaboration.*

ORD response: ORD is working with many Federal partners (as well as State and local governments and Tribes) with the common goal of protecting and promoting children's health and development. Goals of the Federal Taskforce for Children's Health Protection (on which the EPA is participating) include elimination of overlap and promotion of synergy by combining expertise across agencies for the benefit of children's health. Partners include the U.S. Department of Education, U.S. Department of Housing and Urban Development, the Centers for Disease Control and Prevention (CDC), and other arms of the U.S. Department Health and Human Services including the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Heart Lung and Blood Institute and NIMHD. ORD is represented on the subcommittee which has proposed a National Action Plan for Reducing Racial and Ethnic Asthma Disparities which is due to be released in 2012, and on the subcommittee proposing strategies for evaluating products and chemicals with which children are most likely to come into contact. Peter Grevatt is the lead for the EPA on this Federal Taskforce and can provide updates for CHPAC as its agenda progresses. As mentioned earlier, SHC plans to support a 2012 RFA to solicit research on how school buildings and practices can be optimized to promote children's health and performance; this RFA was developed in collaboration with the Department of Education. ORD and OCHP are active members of the Interagency Coordinating Committee for NCS and meet regularly with members from CDC, NIEHS and NICHD to help insure that NCS meets the needs of all partner Agencies and is positioned to achieve its overarching goal of understanding environmental impacts (defined broadly) on children's health and development. SHC is working with HUD and the EPA's Office of Sustainable Communities (in additional to national sustainability organizations and community development groups) to develop and apply tools for smart and sustainable community development that promotes health and protects ecosystem services in economically viable and socially equitable ways. CSS is a partner and collaborator in the broader Tox21 partnership between the EPA, NIH Chemical Genomics Center, NIEHS/National Toxicology Program and the U.S. Food and Drug Administration.