



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 15 2012

OFFICE OF
CHILDREN'S HEALTH PROTECTION

Pamela Shubat, Ph.D.
Chairwoman
Children's Health Protection Advisory Committee
Minnesota Department of Health
625 North Robert Street
St. Paul, MN 55155-2538

Dear Dr. Shubat:

Thank you for your helpful letter on prenatal exposures and their implications for children's environmental health. I especially want to thank the members of the Children's Health Protection Advisory Committee's (CHPAC) Prenatal Workgroup for their very detailed set of recommendations for improving our understanding of the impacts of early exposure to environmental contaminants.

The EPA has been committed to improving the protection of children's environmental health for many years. As your letter points out, environmental exposures through the mother to the developing fetus can have a profound effect on the future life of a child.

In response to your recommendations covering four diverse areas including: policies and practices; incorporation of social determinants of health and consideration of environmental justice; prenatal research; and communication with the public; let me assure you that EPA will continue to focus on how we best address and respond to environmental threats that our children are exposed to prenatally. The attachment to this letter provides detailed responses to your specific recommendations.

Through the assistance of our Office of Children's Health Protection, I look forward to continuing to work with you to improve the health of every American child.

Sincerely,

A handwritten signature in blue ink, appearing to read "P. C. Grevatt".

Peter C. Grevatt, Ph.D.
Director
Office of Children's Health Protection

cc: Michael Firestone, Martha Berger/OCHP/OA
Lek Kadeli, Ramona Trovato, Robert Kavlock, Sally Darney/ORD
Diane Henshel/RAF
Wendy Cleland-Hamnett, OCSPP

Attachment – Detailed Responses to CHPAC Recommendations re: Prenatal Exposures

I. Update Policies and Practices to Address the Prenatal Period

CHPAC recommends that EPA update its policies and practices throughout the agency to address the prenatal period.

- a. **CHPAC recommends that EPA and its federal partners expand biomonitoring for the prenatal period and use such data to identify chemicals that require attention.**

Neither the prenatal nor early childhood periods are included in the national biomonitoring program at the Centers for Disease Control and Prevention (CDC). The national biomonitoring program should be capable of detecting prenatal exposures to chemicals in broad use and those in children's environments, as part of a program to ensure chemical safety. Consideration of chemicals detected in maternal blood would provide an additional useful perspective.

EPA Response:

An EPA workgroup chaired by the Office of Research and Development (ORD) meets regularly to recommend chemicals for inclusion into CDC's National Health and Nutrition Examination Survey (NHANES), including those of concern with respect to maternal and lactational exposures. ORD research is contributing to an increased understanding of the methods and priorities for conducting biomonitoring in pregnant women. EPA will share these results with CDC in order to inform their decisions on how best to incorporate this work into NHANES in the future.

The Children's Environmental Health and Disease Prevention Studies (co-funded by EPA and the National Institute for Environmental Health Studies - NIEHS) continue to generate biomonitoring data for chemicals of interest in pregnant women and young children. Strategic use of longitudinal study designs has enabled some of these Centers to relate biomonitoring data in pregnant women to health outcomes in their children. A number of statistically significant associations have been reported between prenatal exposures to selected pesticides and toxic substances, and to air pollution and a variety of neurodevelopmental and airway inflammation outcomes. Some cohorts of these children are now reaching the age of puberty. With EPA's continued commitment to this program, it will be possible to examine potential associations between prenatal and early life exposures to certain endocrine disruptors and the age of onset of puberty and evaluate whether effects seen in animal models may also be present in children.

Additionally, OCHP will raise consideration of expansion of U.S. biomonitoring efforts with respect to the prenatal period through the President's Task Force on Environmental Health and Safety Risks to Children.

- b. **CHPAC recommends that EPA consistently consider the prenatal period when developing standards and guidelines for allowable concentrations of chemicals in environmental or exposure media and when adopting toxicity values such as reference doses or cancer risk values. Further, CHPAC recommends that EPA adopt methods to protect against potential effects of prenatal exposures in cases where data are lacking to fully assess the significance of such exposures.**

When sufficient data are not available, it may be appropriate for EPA to adopt adjustment factors to account for the uncertainties of the database and for concerns about exposure, vulnerability, or sensitivity. CHPAC believes that the significance of exposures during the prenatal period is not adequately addressed by the current use of adjustment and uncertainty factors.

EPA Response:

EPA appreciates the CHPAC recommendation to consistently consider the prenatal period when developing standards and guidelines for allowable concentrations of chemicals in environmental or exposure media and when adopting toxicity values such as reference doses or cancer risk values, and the Agency is currently involved in several activities to address this recommendation.

The Exposure Oversight Committee of EPA's Risk Assessment Forum (RAF) is considering establishing a Technical Panel to address prenatal exposures. The initial activities of the Technical Panel would conduct a review of the literature on prenatal exposure to chemicals and consider a path forward. The Oversight Committee will consider this CHPAC recommendation as they weigh options for proceeding on this activity.

Additionally, the Human Health Risk Assessment (HHRA) program within ORD's National Center for Environmental Assessment (NCEA) produces Integrated Risk Information System (IRIS) toxicity assessments, Integrated Science Assessments for criteria air pollutants, and Provisional Peer Reviewed Toxicity Values for Superfund assessments, all of which systematically include consideration of adverse outcomes of early life exposures in the development of toxicity values or cancer values. The assessment of potential effects from early life exposures, such as developmental and reproductive health studies in animals and humans, also consistently factor into non-cancer evaluations of susceptibility and the strength of the evidence in the database. In cases where these types of data are absent, this is clearly reflected in the discussion of the uncertainty in the database.

EPA considers cancer risk from *in utero* exposure on a case-by-case basis, based on available data. The available data for prenatal exposure are more limited than for postnatal exposure for most chemicals and are typically more difficult to measure. However, the agency is currently taking steps to address this important issue. For example, EPA is currently developing a state-of-the-science health assessment for inorganic arsenic that will include an analysis of cancer risk from *in utero* exposure. This analysis is expected to undergo NRC review and will be used as a case study for future assessments for evaluating cancer risks from *in utero* exposure. A document that will inform this assessment, *Life Stage Susceptibility to Arsenic: A*

Review of Emerging Evidence, is in draft form. The timeline for peer review of the assessment is currently under consideration.

The HHRA program is planning to review the California EPA (CalEPA) analysis of cancer risk from prenatal and early life exposures, in addition to any other relevant data, to develop a more comprehensive evaluation of differences in susceptibility. It is expected that review of the CalEPA analysis and other relevant data will be completed in 6 months. This information will be used to inform the IRIS program's approach to evaluation of early life-stage susceptibility in its future cancer assessments.

c. **CHPAC recommends that EPA improve the knowledge base for prenatal exposures to support chemical safety assessment.**

Strategies are needed to improve the knowledge base for assessment of the safety of environmental agents during the prenatal period for use by the agency and the public. EPA should incorporate data streams relevant to prenatal exposures in chemical assessment and prioritization. One example is human bioaccumulation, which leads to maternal body burdens and then to prenatal exposures. For agents commonly present in environments and relevant to prenatal exposure, chemical safety testing is critical. EPA should require testing for chemicals or agents that are found in environments that contribute to prenatal exposures.

EPA Response:

EPA already requires developmental and reproductive toxicity testing data for all food use pesticides under 40 CFR Part 158 Subpart F - Toxicology as well as applicator exposure and post-application exposure data under Subpart K. The protocols for the toxicity tests include:

870.3550 - Reproduction/Developmental Toxicity Screening Test
870.3650 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test
870.3700 - Prenatal Developmental Toxicity Study
870.3800 - Reproduction and Fertility Effects

In February 2012, EPA's Office of Pollution Prevention and Toxics (OPPT) released TSCA Work Plan Chemicals: Methods Document which describes important factors and related data sources that can be used to identify potential candidate chemicals for near-term review and assessment under the Toxic Substances Control Act (TSCA). The Agency intends to use these TSCA Work Plan Chemicals to help focus and direct the activities of the Existing Chemicals Program in OPPT. Important factors include:

- Chemicals identified as potentially of concern for children's health (e.g., chemicals with reproductive or developmental effects)
- Chemicals identified as persistent, bioaccumulative, and toxic (PBT)

- Chemicals identified as probable or known carcinogens
- Chemicals used in children's products
- Chemicals used in consumer products
- Chemicals detected in biomonitoring programs.

Many efforts are underway to improve the knowledge base for assessments related to prenatal exposures. EPA, working with OECD has revised and enhanced the 1998 multigenerational testing guideline studies (US EPA 870.3800: Reproduction and fertility effects and OECD 416: Two-Generation Reproduction Toxicity Study) in order to better identify potential reproductive and developmental effects that occur as a result of gestational and lactational exposure. In the new guideline (OECD. 443: Extended One-Generation Reproductive Toxicity Study), several improvements and clarifications to the study design provide more flexibility and stress the importance of starting with existing knowledge, while using in-life observations to guide and tailor the testing. The new test provides an evaluation of the pre- and postnatal effects of chemicals on development as well as a thorough evaluation of systemic toxicity in pregnant and lactating females and young and adult offspring. In addition to the endpoints examined in the previous multi-generation guidelines, the extended one-generation study includes a number of new endpoints that enhance the sensitivity of the test to detect reproductive and developmental effects. Furthermore, this guideline provides an evaluation of the potential developmental neurotoxicity and immunotoxicity related to the test chemical. Finally, this guideline provides direction for the use of absorption, distribution, metabolism and excretion (ADME) information of the test chemical during gestation and lactation further enhancing the overall understanding of the perinatal toxicity of the chemical.

This new protocol has been discussed broadly with the regulatory and international communities. Several recent publications address the technical difficulty and feasibility of this protocol as a replacement for the current multigenerational study design, and others are imminent. In addition, there are at least two chemicals under review by the Agency that have employed the extended one-generation reproductive test successfully. The development of this protocol is discussed in Cooper et al., 2006 (A tiered approach to life stages testing for agricultural chemical safety assessment. *Crit Rev Toxicol.* 2006 Jan;36(1):69-98) and Cooper, 2009 (Current developments in reproductive toxicity testing of pesticides. *Reprod Toxicol.* 2009 28(2):180-7).

In addition, HHRA scientists have helped organize three workshops in the past three years addressing prenatal exposure related to non-mutagenic mechanisms for cancer and non-cancer risks. These workshops have informed EPA efforts to link prenatal exposures to postnatal manifestation of disease. EPA continues to collaborate with NAS and NIEHS on this and other risk assessment issues.

- Mammary Gland Evaluation and Risk Assessment Workshop (Oakland, California, November 16-17 2009)

- Early Indicators of Disease: Use of *in utero* and Post-Natal Indicators to Predict Health Outcomes Later in Life (Washington, DC, Oct 14, 2010)
- The Role of Environmental Chemicals in Diabetes and Obesity: A National Toxicology Program Workshop (Research Triangle Park, NC, Jan 11-13, 2011)

These workshops noted above brought together broad cross sections of stakeholders to examine the link between prenatal exposures and the health effects that manifest later in life. Two resulting papers have summarized these workshops.

- Environmental exposures and mammary gland development: state of the science, public health implications, and research recommendations. (Environmental Health Perspectives 2011 Aug;119(8):1053-61) This paper addresses breast cancer risk due to early life exposures.
- Predicting Later-Life Outcomes of Early-Life Exposures (Environmental Health Perspectives, submitted)

EPA's Virtual Embryo research initiative is building a novel computational framework for developmental toxicity that comprises tools and models focused on two aspects: knowledge in the form of data and information about specific developmental processes and signaling pathways; and cell-based computer simulations of developing systems. The virtual tissues knowledgebase, under construction for this project, is focusing on extracting information relevant to developmental processes in general and prenatal developmental toxicity in particular. Strategic plans and progress for EPA's Virtual Embryo project can be followed on a website linked to the National Center for Computational Toxicology (NCCT) at <http://www.epa.gov/ncct/v-Embryo/>.

d. **CHPAC recommends that EPA consider all of the hazards and associated health endpoints in chemical screening and assessment that result from prenatal exposure.**

EPA and other entities emphasize reproductive and developmental effects as sole outcomes that are important for children. Such an approach will miss other important adverse health outcomes. Prenatal exposure can contribute to a variety of conditions and diseases during childhood including effects on neurodevelopment, lung development, respiratory function, immune function, and hormonal systems. These exposures can also contribute to increased risk of diseases later in life.

EPA Response:

EPA recognizes the importance of this emerging issue in environmental health science and considers research on this topic a high priority. ORD would be happy to discuss its strategies for addressing this issue in more detail at a future CHPAC meeting. As mentioned above, the new "extended one generation" test begins dosing before birth (pre-conception exposures) and continues it through pregnancy into adulthood. It includes a range of health outcomes such as neurodevelopmental and immunological assessments in the developing offspring. To evaluate the potential for longer term impacts, ORD is also developing and evaluating an animal

model which determines the consequences of prenatal exposures on growth, organogenesis and metabolism in adult animals at various ages. Such changes (thought to be epigenetic) could contribute to a propensity for obesity, hypertension, and cardio-vascular disease in the offspring (see response from ORD to Dr. Shubat's December 21, 2011 letter to the Administrator for more detail). Finally, several of the Children's Centers mentioned previously are examining this theory in children's cohorts, including potential impacts of air pollution and endotoxins on asthma causation and using early markers of airway inflammation, and of endocrine disruptors on reproductive organ and tract development. Also, grantees of a 2005 STAR solicitation on "Early Indicators of Environmental Disease" have demonstrated postnatal impacts of maternal exposure to air pollution on subsequent risks of airway inflammatory disease in a carefully controlled primate model. These and other early indicators were featured at a grantee workshop on March 8, 2012, the proceedings of which will be posted on EPA's National Center for Environmental Research (NCER) website in the near future, along with their final reports.

With respect to current risk assessment practice, IRIS health assessments and Integrated Science Assessments for criteria air pollutants routinely examine both animal toxicity data and epidemiological data. Chemical-induced disease outcomes and chemical induced exacerbation of disease are considered in these health assessments when data are available.

- e. **CHPAC recommends that EPA consistently include the prenatal period in methods for safety testing of chemicals, including traditional methods that rely on whole animals, as well as the "robot" methods that rely on high or medium throughput strategies and testing of narrow responses. CHPAC also recommends that EPA ensure that the validation for any of the newer "robot" or high throughput or other such methods include the prenatal period as well as the perturbation or endpoints that may occur as a result of prenatal exposures.**

While ToxCast and other high throughput testing strategies will yield a great deal of information, it is important to ensure that these techniques have the capability to detect effects of prenatal exposures. CHPAC is concerned that the current approach to validation of ToxCast and related "robot" or high throughput methods does not adequately reflect either exposures during the prenatal period nor all of the kinds of perturbations or endpoints that may occur as a result of prenatal exposures. Consequently, they may produce false negatives and allow chemicals where prenatal effects may be important to be viewed as "safe." One approach would be to require whole animal, multigenerational toxicity studies in order to develop a robust source of prenatal toxicity data for comparing, correlating, and interpreting results from the next generation of toxicity testing developed by EPA and its partners. Perhaps there are other options as well. A robust option that addresses the prenatal period is needed, and, so far as CHPAC has been able to determine, has not yet been identified.

EPA Response:

EPA recognizes limitations of current test designs and is working with our domestic and international partners to improve both whole animal testing schemes and predictive toxicity pathway research derived from ToxCast. EPA recognizes that high throughput methods require in life validation including strategically designed whole animal short term protocols (such as developed for the endocrine disruptors program) and selective application of the extended one-generation test described above to the chemicals of greatest concern based on exposure and screening results.

As explained in more detail in EPA's response to Dr. Shubat's December 21, 2011 letter to the Administrator, ORD is working to incorporate knowledge of developmental exposures and outcomes into high throughput screening (HTS) of chemicals in the Chemical Safety for Sustainability Program (CSS). This research is occurring at multiple levels of complexity including development of *in vitro* assays, susceptibility biomarkers, and *in silico* models (e.g., the Virtual Embryo). In the near-term, this research can help prioritize large numbers of chemicals for targeted testing or lifestage-specific exposure assessment based on *in vitro* signatures that may be indicative of potential developmental toxicity.

For example, HTS data are 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.

Companion research in the Sustainable and Healthy Communities Program (SHC) is developing animal models to "ground-truth" results of *in vitro/in silico* predictions and evaluate potential mechanisms. Finally, EPA and NIEHS supported Children's Centers and other agency grantees are evaluating health outcomes subsequent to *in utero* exposures in longitudinal studies involving children and families in both urban and rural scenarios.

- f. **CHPAC recommends that EPA develop criteria for use of screening tests that account for the limitations of the tests for identifying chemicals that may adversely affect the prenatal life stage.**

It is important that the implications of screening results be carefully considered. We understand that EPA intends to use a positive result (i. e., showing an effect) in a screening test to refer a chemical for additional testing using broader methods. Conversely, agents found to be negative (i.e. lacking any effect) during screening would receive no further testing in this paradigm. EPA would fail to follow up on false negatives. CHPAC is concerned that under this approach EPA may not

recognize false negatives and, consequently, not be protective for children; particularly for results of prenatal exposures because of the lack of complete coverage of early life stages by the newer, faster screening methods.

EPA Response:

As mentioned earlier, HTS data are being collected toward a pathway-based integrative strategy that testing in sensitive systems including mouse embryonic stem cells, human pluripotent stem cells (derived from adult tissues), and zebrafish development. In this research, we are striving to define the suites of in vitro assays that accurately flag both positive and negative results for prenatal developmental toxicity and the adverse outcome pathways that are most informative of a potential hazard. The sensitivity and specificity of these computational models is tuned to optimize true positives and suppress false negatives. Exploratory research is being done to qualify the results from HTS for both positives and negatives. Regulatory toxicology is still working out how to use HTS data for risk assessment and what else to require as HTS interpretation is qualified. ORD can address false negatives by expanding its HTS assay portfolio with new assay development and computational methods.

- g. **CHPAC recommends that EPA develop metrics to account for the combined burden of prenatal exposure.**

Such metrics could then be used to help track and study the overall burden of exposure during the prenatal period and its effects. The combination of chemicals that may accumulate during the prenatal period is a concern. It is not just individual chemicals but the burden of all these chemicals acting together that will affect the development of a child and contribute to health effects.

EPA Response:

An existing RAF Cumulative Risk Assessment Technical Panel is currently considering a variety of exposure scenarios in a Cumulative Risk Assessment Guideline that is currently under development. The RAF Cumulative Risk Assessment Technical Panel will consider the recommendations of the CHPAC as they address the potential impacts of cumulative prenatal exposures in development of the guideline.

Additionally, ORD's SHC research program is working to develop metrics that may be used to help track and study the overall burden of exposure during the prenatal period and its effects. These indicators, in combination with the biomonitoring research program in CSS, may identify effects as a result of combinations of chemicals to which very young children may be exposed during the prenatal period.

- h. **CHPAC recommends that EPA work with the National Institute for Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA), and industry to develop mechanisms to assure**

protection of men and women in the workplace from exposures that may impact the workers during the preconception and prenatal period.

EPA Response:

The President's Task Force on Environmental Health and Safety Risks to Children, co-chaired by EPA and HHS, provides the opportunity for multiple federal departments and agencies to address priority children's environmental health issues. In response to the CHPAC recommendation, EPA has initiated a discussion with the Department of Labor, OSHA and NIOSH to explore opportunities to give greater consideration to potential prenatal exposures through the communication and enforcement of current worker protection standards.

The Agency's Office of Pesticides Programs (OPP) considers adverse reproductive and developmental effects for all pesticides as part of its risk assessment process. The process includes evaluation of toxicity studies with special emphasis on impact of exposure during the preconception and prenatal period for all occupational and consumer uses of pesticides. When adverse reproductive and or developmental effects are identified, the risk assessment is then based on doses from animal studies where these effects are observed. Personal protective equipment (PPE) during applications and safe reentry periods into treated areas are then assigned for inclusion on pesticide labeling based on real world exposure data.

The safety standard established in the risk assessment process assumes compliance with pesticide labeling. As a means of evaluating compliance, incident data from sources such as NIOSH's Sentinel Event Notification System for Occupational Risk (SENSOR) are evaluated for the potential adverse impacts from use or misuse of specific pesticides. EPA's pesticide program collaborates with NIOSH and provides funding for states to provide data for SENSOR. This surveillance work focuses on acute pesticide poisoning in an occupational setting, and identifies routes and conditions of exposure. EPA uses this information to identify areas of concern for workers, including those exposed during the preconception and prenatal period.

Other concerns involve the proper use of PPE. Currently, EPA is participating in NIOSH's Personal Protective Equipment Selection, Use and Expectations: Personal Protective Technology Stakeholder Meeting and Workshop developed to address work-related injury and illnesses and advancing the state and knowledge of personal protective technology. We have also presented at NIOSH's Pesticide Handler Personal Protective Equipment Seminar Series a discussion of PPE assignment for EPA pesticide labels. The seminar series is well attended by pesticide trainers, university and state employees involved in pesticide training and other interested stakeholders. In addition we have also reviewed the NIOSH pesticide PPE survey designed to address barriers to the use of PPE by greenhouse and nursery workers.

OPP is also developing regulatory proposals to better inform and educate farmworkers and pesticide handlers on risks to themselves and their families from their occupational exposure to pesticides. These proposals focus on safety training and ways workers can limit take home exposure to their families. Additional

proposals focus on reducing occupational exposures to handlers and workers, including pregnant women.

In a local effort, EPA has developed outreach methods to reach and educate pregnant workers and workers of childbearing age and their spouses or partners on specific pesticide risks during pregnancy. The agency also provides information on how to protect families from pesticide exposures. Radio Public Service Announcements (PSAs) and a culturally sensitive brochure in Spanish with information on pesticide safety specifics are being provided to women who are pregnant or may become pregnant and their spouses or partners. In a later phase, EPA plans to work with migrant health organizations and worker advocacy groups to develop and pilot a curriculum and training class specific to women of child bearing age.

In addition, the HHRA program recently established a memo of understanding with NIOSH to establish a partnership to advance the protection of environment and public health. EPA looks forward to the additional opportunities this will provide to protect children from potentially harmful prenatal exposures.

II. Incorporate Social Determinants of Health and Environmental Justice into Programs and Policies

a. CHPAC recommends that EPA begin to quantify and incorporate social determinants of health into its programs and policies, including risk assessment and risk management.

Health disparities are closely linked with social and economic disadvantage. The influence of social determinants, including income, education, occupation, race/ethnicity, and an individual's environment, begins even before birth. The unequal distribution of environmental exposures and resulting burden of disease is inextricably linked to social determinants of health. For example, the effects of social determinants such as stress, on birth weight, one common metric for the prenatal period, are well established. Emerging research on the role of stress in environmentally related health condition underscores the need to fully consider the social determinants of health.

Research has shown how a woman's health during pregnancy affects her newborn's life chances and long-term health risks and how social characteristics such as income, education, race/ethnicity, and occupation can significantly impact health. Some of the adverse effects that develop from exposures in early stages of human development are difficult to overcome later on in life. Social conditions also have an impact on life-long health, including that of future generations and, therefore, need to be more thoughtfully researched as well as integrated into policy decisions.

EPA Response:

EPA's Office of Policy is developing an additional chapter for its Guidelines for Preparing Economic Analyses focusing on environmental justice, children's environmental health, and other distributional considerations. The chapter acknowledges the role of economic factors and health outcomes as well as the intersection between environmental justice and children's environmental health, and the challenges these pose for analysis. OP will consider CHPAC's recommendations in the development of this chapter.

ORD's research plans emphasize the importance of understanding and considering social determinants in risk assessment and remediation. SHC includes a project dedicated to this topic which is designed to meet research and science objectives laid out in EPA's Environmental Justice Plan (Plan EJ 2014). The SHC project entitled "Securing and Sustaining Environmental Justice" includes ongoing extramural research solicited to address the influence of social and economic factors combined with chemical risks on human health, particularly at the community and family level. This aspect of cumulative assessment is also a feature of the HHRA program evaluating approaches to assess chemical and non-chemical stressors. SHC is also leading a cross-ORD effort to coordinate research that supports Plan EJ 2014 and its principals across all its programs. The Office of Environmental Justice participates actively in this workgroup.

The SHC research strategy also includes extramural research conducted in collaboration with the National Institute of Minority Health and Health Disparities (NIMH) which includes emphasis on the built environment in research objectives of their Centers of Excellence in Environmental Justice grants program. Some of these grants specifically address children's health, and all are designed to build community capacity for research and decision making. A discussion is planned for the next CHPAC meeting about these newly initiated research efforts on social determinants of health disparities and environmental justice.

Intramural ORD research is also addressing issues relevant to environmental justice including the extent to which disadvantaged communities and groups may suffer disproportionate risks from air pollution resulting from wild fires, living near roadways, and other scenarios. SHC is also working with Community Action for Renewed Environment (CARE) grantees to build useful tools for improved community decision-making. Finally, ORD has been working closely with EPA's Office of Air and Radiation to develop and align research with a Federal Action Plan to Reduce Minority and Ethnic Asthma Disparities. This plan was developed in collaboration with several other Federal agencies.

- b. **CHPAC recommends that OCHP work in collaboration with the Office of Environmental Justice on issues of research, policy and action to address health disparities, specifically in the prenatal period.**

Creating a more comprehensive, sustainable framework to achieve environmental justice will require public participation and building on existing science and successful partnerships. EPA's Plan EJ 2014⁴ outlines a number of strategies to empower disenfranchised communities. This Plan can be used to expand the definition of vulnerable populations to include women who are or may become

pregnant, infants, children, and the unborn. Linking environmental justice priorities for action with the OCHP's mission to protect children from environmental risks would leverage resources and expertise to reduce health disparities and promote environmental justice throughout life.

EPA Response:

OCHP has been working on an intra-Agency team which is developing EJ technical guidance. OCHP has pointed out to the workgroup that the burden of elevated levels of environmental exposures (as compared to adults) and resulting health problems is often borne disproportionately by children living in low-income communities and communities of color.

For the past 4 years, EPA's Office of Environmental Justice (OEJ) has been working to develop a strong science foundation for understanding environmental justice/environmental health disparities, with the purpose of integrating EJ in assessments conducted in the context of informing decision making. Specifically, OEJ identified chronic psychosocial stress as one of a number of factors that likely contribute to disproportionate environmental health impacts. They have also identified other social determinants of health such as capacity to participate in decision making and housing.

Recognizing that chronic exposure to psychosocial stress is a relatively novel concept in environmental health protection, OEJ is working in partnership with the Office of Research and Development's National Center for Environmental Research (ORD/NCER) to create an understanding among environmental health scientists about chronic psychosocial stress, the biological pathways through which stress independently impacts health, and therefore the pathways through which interactions with environmental hazards may occur. Below are specific activities that they have undertaken.

- In 2010, OCHP was among many partners who hosted the EJ science Symposium "Strengthening Environmental Justice Research and Decision Making: A Symposium on the Science of Disproportionate Environmental Health Impacts." This meeting featured a discussion session on chronic psychosocial stress. The purpose of this session was to elicit discourse about biological pathways for stress, highlight emerging toxicological research on interactions between stress and environmental hazards, and discuss how adverse environmental conditions attributable to pollution may contribute to chronic psychosocial stress in communities with environmental justice issues.

In addition to the topic of psychosocial stress, similar panels dealt with other social determinants of health such as housing and community capacity to participate in decision making.

- In 2011, OEJ published two EPA commissioned papers in a special issue of the American Journal of Public Health as a follow-up to the Symposium: (1) "Critical Biological Pathways for Chronic Psychosocial Stress and Research Opportunities to Advance the Consideration of Stress in Chemical Risk Assessment"; and (2) "Community Stress, Psychosocial Hazards, and EPA Decision-Making in Communities Impacted by Chronic Technological Disasters".

The former paper provides a condensed review of the science how chronic stress impacts key biological pathways that are also impacted by environmental hazards, and provides insight into the types of research that would help advance knowledge in this area and its application in risk assessment and decision-making. The second paper explores how environmental contamination, a common denominator with many stakeholder communities may drive psychosocial stress.

EPA also commissioned papers on the other topics such as community capacity to participate in decision making and housing in this supplement. These and other papers can be accessed at: <http://ajph.aphapublications.org/toc/ajph/101/S1>.

- In May 2012, OEJ is co-hosting a workshop with ORD/NCER with the objective of further advancing the discourse within EPA on the interactions between social stressors and environmental hazards. This meeting will feature presentations and discussions on biological pathways of stress, and emerging epidemiological and toxicological studies of interactions between stress and environmental hazards. Some of the presentations will feature emerging evidence of this type of interaction as it affects adverse outcomes related to environmental exposures that are prevalent among children such as asthma and cognitive deficits. The target audience for this workshop is EPA's risk assessors, health scientists and toxicologists, who will play a central role in determining how the Agency utilizes the emerging research in decision making.

III. Design and Disseminate Messages through Diverse Partnerships

CHPAC recommends that OCHP lead EPA in creating and implementing an agency-wide, nationally consistent outreach and communications plan about prenatal environmental exposures.

EPA should engage with diverse partners including professional health care provider organizations, community-based organizations, and academic partners to create effective messaging for the public. Information can empower the public so they can participate in the development of public policies related to the environment and health and take individual actions to avoid or reduce harmful exposures (e.g., metals, pesticides, solvents, plastics, air pollutants, tobacco smoke). Models for messaging about reducing risks during the prenatal period have been created by the March of Dimes and past efforts of EPA. EPA can build upon these effective examples, leveraging resources through collaborations with organizations that produce and disseminate health messages for pregnant women.

- a. **CHPAC recommends that EPA partner with experts in public health education and social marketing to create effective agency-wide communication strategies that produce culturally sensitive messages for health providers and women and their families.**

Partnerships between EPA and other federal agencies such as the Maternal Child

Health Bureau provide opportunities for cross-disciplinary development of messages about how to prevent prenatal exposures.

EPA Response 11:

EPA appreciates the CHPAC recommendations for communications planning, consistent and scientifically-based national messaging, and evaluation of these efforts. The Agency has a number of ongoing efforts with experts in public health education and social marketing to develop effective public communication strategies on priority actions related to children's environmental health. For example, EPA recently partnered with the Ad Council to develop messages related to the continuing importance of protecting children from the hazards of lead based paint. The Office of Children's Health Protection is working with the Pediatric Environmental Health Specialty Units and several other organizations committed to prenatal health to identify the opportunities for crafting messages based on current research, disseminate those messages to communities most in need, and create a broader strategy to ensure that health providers are trained to recognize, prevent and reduce harmful prenatal environmental exposures. OCHP is also exploring opportunities to partner with ACOG to increase the availability of effective messaging for expectant parents regarding the importance of avoiding potentially harmful environmental exposures during the prenatal period. OCHP is also working to establish partnerships with other federal agencies including the Administration for Children and Families and the Health Resource Services Administration to enhance communication and outreach to parents regarding the importance of creating a healthy environment for children during the prenatal period. We will consider the CHPAC recommendations as we move forward with these efforts.

- b. **CHPAC recommends that EPA use existing partnerships and create new ones to effectively disseminate messages to women who are or may become pregnant, their families and their providers.**

Integration of messages with existing networks such as the National Healthy Homes, Healthy Babies Coalition⁷ and electronic media such as text4baby , Health 2.0 , Fish-Facts.org, and other web-based and new media approaches would offer opportunities to reach targeted populations efficiently. Public health professionals, health care providers and especially Pediatric Environmental Health Specialty Unit (PEHSU) staff are key messengers who can identify at-risk populations, provide anticipatory guidance and education about environmental exposures, and empower communities to take precautionary action. Messaging efforts could replicate strategies used in successful public health campaigns such as the stop smoking campaigns to raise awareness and provide action steps.

Partnerships between EPA and community-centered care would present another opportunity for dissemination of messages by health care providers in diverse and underserved settings, including urban, rural, and tribal communities.

Peer-reviewed publications that discuss clinical approaches to the translation of

research findings into practice through the identification and management of environmental health issues pre-conceptually and prenatally would also provide a means for reaching public health professionals and health care providers.

EPA Response:

As mentioned above, EPA continues to partner with HHS on our support for the Pediatric Environmental Health Specialty Units, and an important part of this work going forward will be to craft effective messages from health care providers to expectant parents on the importance of creating healthy environments for children, including during the prenatal period. EPA is currently actively engaged in partnerships to explore opportunities to enhance community centered care in diverse and underserved settings, including urban, rural and tribal communities, including Alaska Native Villages. We will consider the CHPAC recommendations as we continue in these efforts. One additional example of an on-going partnership focused on preventing potentially harmful prenatal exposures involves the development of the Navigation Guide, an effort led by the Program on Reproductive Health and the Environment at the University of California, San Francisco. This methodology systematically evaluates data on environmental exposures and reproductive health to support prevention efforts of clinicians and public health policy makers (Woodruff, et al., 2011, An Evidence-Based Medicine Methodology to Bridge the Gap Between Clinical and Environmental Health Sciences, Health Affairs, 30: 931-937).

c. **CHPAC recommends that EPA evaluate the effectiveness of its communication messaging.**

Evaluation should include whether the message was culturally sensitive, if the message was disseminated through media appropriate for the targeted audience, and if knowledge and behavior of individuals and communities, as well as policies were modified to reduce or eliminate prenatal environmental hazards. Empowering the public with information on these environmental hazards can create a constituency that demands public policy that protects the environment and the health of future generations.

EPA Response:

EPA appreciates the importance of evaluating the effectiveness of messages that are developed and disseminated to determine whether they had the desired effect of informing the knowledge and behavior of individuals and communities to enhance protectiveness of children's environmental health. This is particularly important during times of increasingly constrained budgets. EPA would welcome recommendations from the CHPAC regarding strategies that have been effectively employed to measure behavior change resulting from messaging on key public health issues.

IV. Address the prenatal period, key outcomes, and mechanisms in research priorities

CHPAC recommends that EPA continue to conduct, fund, and promote research on the effects of prenatal exposures, through continued support for the EPA/NIEHS Children's Environmental Health Research Centers, its own research, and partnerships with other research funding entities.

a. CHPAC recommends conducting research on the effects of pre-conception exposures.

The pre-conception time period has received limited research attention, though there is evidence that metals such as chromium III can have effects after pre-conception exposure in mice, including epigenetic changes, increased cancer risk, and hormonal changes. Other agents to be studied include those that bioaccumulate or have long half-lives in the body, such as some metals (e.g., lead, mercury) and halogenated compounds (e.g., PCBs, dioxins).

EPA Response:

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 SHC's Children's Health project which includes not only the Children's Centers Program mentioned previously, but also intramural research that is developing and using animal models and protocols specifically to evaluate the impact of prenatal exposures on later health impacts. These studies examine impacts on multiple systems that contribute to the development of metabolic disorders (e.g. diabetes, hypertension) later in life, and track neurodevelopmental outcomes during neonatal and pubertal periods. Several EPA researchers are leaders in the emerging field called "Developmental Origins of Health and Disease" and are key players in national and international meetings on this subject. While focusing on chemical exposures of interest to EPA, the model is also incorporating non-chemical factors such as nutrition and stress and their relative contributions to health throughout life. The expectation is that such animal models can be used to test hypotheses generated by epidemiological research and thereby address causation and mechanisms

Research to advance our understanding of how chemicals interact with important biological processes inside the embryo, pregnant mother, or developing child is also underway 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.

- b. **CHPAC recommends that EPA focus research attention on epigenetic effects resulting from prenatal exposures.**

Epigenetics changes are potentially heritable changes to the genome that do not involve changes in DNA sequence, including DNA methylation, histone modification, and microRNA changes. These changes can suppress or stimulate gene expression, which can lead to changes in health endpoints. Epigenetic mechanisms may explain how environmental toxicants impact the genome early in fetal life and program future disease development in current and future generations. For example, increased DNA placental methylation patterns have been associated with abnormal fetal growth and environmental factors may influence DNA methylation during the prenatal period.

EPA Response:

EPA is well aware of the potential role of epigenetic mechanisms which have the potential to “reprogram” development and metabolism. The National Institute for Environmental Health Sciences has funded extensive research on this topic. Agency research efforts aim to complement these larger efforts by applying new molecular and imaging technology to address specific hypotheses in the context of HTP screening program in CSS. In SHC, specific epigenetic hypotheses are also being addressed some of the Children’s Centers projects, and in the in-house research evaluating an animal model for long term impacts of prenatal exposures described previously.

- c. **CHPAC recommends that EPA support and conduct research that accounts for mixture effects, to investigate how multiple contaminant exposures occurring during pre-conception and prenatal periods affect biological systems and lead to disease development.**

Research priorities should recognize that humans experience multiple exposures to multiple chemicals, often at low dose levels, throughout all life stages, including the pre-conception and prenatal stages. For example, data show that women are exposed to multiple phthalate chemicals. In animal studies, prenatal exposures to mixtures of phthalate chemicals leads to compounded health outcomes as compared to single agent exposures.

EPA Response:

As detailed in ORD’s response to Dr. Shubat’s letter dated December 21, 2012, 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. In vitro models are also being used to evaluate the potential for PFCs to behave additively with respect to their mechanism of action (i.e., activation of peroxisome proliferator activator receptor alpha, a key nuclear receptor in the biological response to PFCs).

Furthermore, research in SHC is evaluating age-specific exposure factors to identify how and where children come into contact with various chemical stressors, and how non-chemical stressors (social determinants) may exacerbate their responses to chemical stressors. The long range goal of SHC is to provide tools and guidance whereby communities and individuals can not only avoid harmful exposures to multiple stressors but also participate actively in health promoting activities and behaviors.

Finally, research in the Children's Centers program is also considering cumulative impacts of multiple chemicals to which their cohorts are exposed in community-specific contexts. And several grantees are reporting on statistical models for evaluating complex exposures.

d. **CHPAC recommends that EPA focus research attention on chronic diseases that are increasingly observed in children including but not limited to neurodevelopmental disorders, obesity, and allergies/asthma.**

We need to know what exposures contribute to these disorders and how effects occur. The prevalence of neurodevelopmental disorders including autism, ADHD, and anxiety is increasing in children without known cause. Early life programming of brain development is extremely important for cognition and neurologic function throughout life. The neurologic system starts to develop in fetal life and continues with important periods of vulnerability throughout early childhood, later childhood, and adolescence.

Childhood obesity is at epidemic proportions in the United States. While exercise and diet play a large role in metabolic programming, many physicians and scientists recognize that some individuals have different metabolic set points that predispose them to gain weight and store fat. Programming of these set points is thought to occur in utero because infants born small or large for gestational age are both at increased risk for obesity later in life.

Both genetic and environmental factors such as dust and pollen contribute to allergic (IgE mediated) disease development, but little is known about how emerging environmental toxicants may contribute to disease development. Childhood allergies, asthma, and eczema are considered atopic diseases that

consistently lead to physician visits and/or hospital admission. Maternal history of allergies and asthma is directly linked to infant outcomes and may reflect both genetic and environmental exposures during the prenatal period. With the rise in these diseases, other environmental factors such as changing pollen concentrations due to climate change, new toxicants found in dust, or exposure to nanoparticles may be contributing to disease development.

EPA Response:

ORD is well aware of these important and emerging issues in children's health as well as national efforts to address them, both in EPA and in our sister Agencies. In addition to the in-house project described above (examining long term outcomes, including metabolic disorder and obesity, stemming from prenatal exposures), research in several EPA/NIEHS Children's Centers is evaluating asthma causation and intervention strategies related to environmental allergens and asthma triggers, relevant to both indoor and outdoor air quality as well as diet. Also, several Clean Air Research Centers (ACE program) are looking at birth outcomes and children's cohorts related to prenatal exposures to chemicals and to allergens. A cluster of STAR grants is examining potential impacts of climate change on environmental allergens (pollen, dust). In-house research is also evaluating near-road conditions and asthma (ACE and SHC) with the goal of informing transportation planning and school/residential siting; and on increased occurrence of wildfires as an additional stressor for asthmatic children along with the need for public health forecasting and intervention programs. We see these issues are cross-cutting and complex in nature, requiring systems approaches and inter-disciplinary expertise.

- e. **CHPAC recommends that EPA engage with populations that are most burdened by environmental exposures and increased disease prevalence in its research activities.**

A growing body of research suggests that there are benefits to conducting environmental health research in partnership with communities. Specifically, low income, underserved communities with disproportionate burdens of environmental exposures and disease should be a priority. Community based participatory research (CBPR) can expand social structures and processes that contribute to the ability of community members to improve health and may enhance translation of research findings into actions to reduce exposures to environmental toxicants and improve public health overall.

We applaud EPA for the continued support for the EPA Community Action for a Renewed Environment (CARE) Program that offers innovative ways for communities to take the lead in research activities, organize, and act to reduce exposures. This program should serve as a model program that can be replicated and expanded.

EPA Response:

ORD is replicating and expanding upon this approach. The EPA/NIEHS Children's Centers continue to fund CBPR research, and the next RFA will include the requirement for a Community Outreach and Translate Core. SHC research is developing public friendly tools, typically in active collaboration with community partners, to support environmental and health planning and community decision-making. Many pilot projects are underway through CARE, as mentioned, and through Regional programs and other partnerships. ORD is also adding staff with expertise in the social sciences and inaugurating capacity building programs to enhance the skills of our scientists for participatory research. Such efforts are being coordinated with EPA Regions, Tribes, the Office of Sustainable Communities and the Office of Environmental Justice as well as OCHP. Finally, the new collaboration with NIMHD (described earlier) is funding participatory research on the fundamental determinants of environmental health disparities.