

## **Hypothesis 6**

**I. Proposed Core Hypothesis:** Exposure to chemicals interacts with the genetics of the fetus/infant/child and other environmental factors to influence adverse outcomes in neuropsychological function including executive function (attention, impulsivity, vigilance, and distractibility), cognition, sensory, motor, social and emotional development, and difficulties in behavioral adjustment (antisocial behavior, poor school achievement, or school failure). Alterations in these functions may express themselves in disorders like autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), mental illnesses such as schizophrenia, mental retardation, and violent criminal behavior.

Environmental exposure to chemicals can interact with the genetic endowment of the individual to modulate the manifestation of toxicity, which may include toxification and detoxification mechanisms, expression of developmental regulatory gene expression, and growth factor and neurotransmitter regulation.

The classes of chemicals that should be measured in the NCS include metals, solvents, cholinesterase inhibitors, organohalogenated compounds, pyrethroids, herbicides, and fungicides.

### **Subhypothesis:**

1. Environmental exposures to chemicals affect expression of growth factors, neurotransmitter, and cytokines which regulate critical processes in neural development, and may result in functional impairments of the nervous systems.
2. Environmental exposures to chemicals interact with genetic and other factors to affect function in specific behavioral domains including executive functions such as vigilance, attention, impulsivity and distractibility; speech and language; cognition; sensory and motor function; social development; emotional development; and aggression.
3. Timing and duration of exposures to environmental chemicals are critical determinants of the pattern and magnitude of the neurobiological effects, resulting in functional impairments.
4. Environmental exposures to chemicals interact with gene expression to result in clinical diagnosis of developmental disorders, including ASD, ADHD, mental illnesses such as schizophrenia, mental retardation, violent criminal behavior, and other mental disorders.

## **II. Workgroup: Neurodevelopment & Behavior**

**III. Contact Person for Proposed Hypothesis:** Deborah Rice, 564-3404, [rice.deborah@epa.gov](mailto:rice.deborah@epa.gov) or Stan Barone, 541-3916, [barone.stan@epa.gov](mailto:barone.stan@epa.gov).

**IV. Public health significance.** Prenatal and early childhood exposures to neurotoxicants, including exposure to environmental chemicals, can result in increased risk for adverse neurodevelopmental outcomes. The timing and dose of exposure to chemical agents, interacting with the genetic makeup of the individual, may result in adverse outcomes such as ASD, ADHD, mental retardation or other major neurodevelopmental disabilities. Neurologic and developmental disorders in children are a major public health concern. The etiology of most mental disturbances is unknown. Autism spectrum disorder appears to be increasing in prevalence (6.7-16.8 per 1000 births; Bertrand *et al.*, 2001; Chakrabarti and Fombonne, 2001) and some neuropsychologic conditions of childhood such as attention deficit-hyperactivity disorder (ADHD) are diagnosed at an epidemic rate (100-150 per 1000 children; Rowland *et al.*, 2002; Barbaresi *et al.*, 2002). Environmental exposures to known neurotoxicants have been shown to affect neuropsychological function including alterations in cognition, sensory, motor, social, emotional development and executive function. Deficits in these functional domains underlie clinically diagnosed syndromes. Many conditions previously thought to be solely of social origin (*e.g.*, ASD) are now known to have biological bases related to gene and

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environmental interactions.

The toxicity of most xenobiotics is not known. For example 3,000 high production volume chemicals (*e.g.*, chemical with over 1 million pounds/year) have not been evaluated for neurodevelopmental effects. Healthy adjustment and normal development is determined by genetics, the total experience of the child, including social factors, and exposure to xenobiotics. Whereas genetic endowment of the population or subpopulations cannot be altered, public health policy can have a significant impact on timing duration, and level of exposure to xenobiotics. The benefits of pollution control have huge monetary and social impact. The monetized benefits from removal of lead from gasoline, for a single cohort of children born in 1998, were estimated as between \$100 billion and 300 billion. (Grosse *et al.*, 2002). The costs of childhood cancer, asthma and behavioral disorders have been shown to be considerable(Landrigan *et al.*, 2002).

### **V. Justification for Large Prospective Study.**

- (1) Many studies of the impact of chemical exposure on functional domains have employed small sample sizes of inadequate statistical power to document effects.
- (2) The prevalence of many clinical syndromes are sufficiently low that large samples are required for detection.
- (3) Adequate power to determine the interactions of chemical exposures, social and physical environmental factors, and gene expression requires a large cohort design. Studies with typical sample sizes necessitate focusing on one (or at most two or three) factors, with any additional potential factors that may influence the outcome treated as confounders.

### **VI. Scientific Merit**

This study will provide sufficient numbers of subjects to determine the inter-relationships between genes, environment, and the additional dimensions of exposure to environmental chemicals. The NCS will allow longitudinal assessment of behaviors that may be predictive of later neuropsychological impairments, as well as allow the development of a large database of age-specific normative performance on a wide variety of intellectual, social, and emotional measures. Analysis of the ontogeny of function in key functional domains will allow a determination of potential early predictors of neurodevelopmental disorders in this population based study. This information could potentially allow identification of children at risk for neuropsychological disorders in the future, and facilitate development of interventive strategies.

In addition to functional determinants, surrogate measures neurobiologically based determinants of neural development may also be useful as early predictors of adverse outcomes. For example, recently research indicates that serological measurement of neurotrophic factors (NTFs) and selected neuropeptides can be used to predict autism spectrum disorders and some other forms of mental retardation (Nelson *et al.*, 2001). This study will allow extensive exploration of the relationship between expression of specific growth and trophic factors involved in nervous system development, biomarkers for genes involved in chemical metabolism, biomarkers of neurotransmitter regulation and expression and their functional consequences, as well as the effects of chemical exposure on expression of gene regulation. Only a study as large as the NCS will allow exploration of all these relevant interactions.

### **VII. Potential for Innovative Research.**

- (1) A significant opportunity of this proposed research is the possibility of studying the effects of the interactions of a wide variety of chemicals on many functional endpoints, in a longitudinal manner. Smaller studies by necessity can only measure a few contaminants, and must treat most of them as “confounders” rather than main study variables.

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(2) This research has great potential to assess how the application of genomic, proteomic and metabonomic technologies may be used for gene and protein expression profiling as predictors of adverse outcomes. Pilot studies in the area of gene and protein profiling with some defined subpopulations which are at risk for development of disorders due to known exposures or genetic predisposition would be very beneficial to demonstrate the utility of this technical approach in a study as large as the NCS.

### VIII. Feasibility

The use of modern technology to assess gene expression is very feasible and relatively economical. Banking of tissue will allow new technologies to be used in the future. Many clinical instruments are already available to assess many of the functional domains that will be of interest in this study. Methodologies exist to measure tissue concentrations of the chemicals of interest at present, although some methodologies are expensive (e.g. PCB congener analysis). Again, tissue banking will allow analysis of new chemicals of interest at a later date.

### Contacts with other workgroups

Deb Rice- exposure workgroup

Stan Barone- Gene Environment work group

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