Potential Impact of the NCS on Priority Health Outcomes

by

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0. INTRODUCTION-SUMMARY

In this report, we present information on ten selected health outcomes explored for this economic impact analysis and the extent to which the NCS might be able to impact those outcomes given NCS core hypotheses, current plans for the study protocol, and the current state of the science. In developing estimates of the extent of impact, we consider various influencing factors including health outcome reductions in the research case studies presented in the April 1, 2004 report on "The Impact of Basic Research on Health Outcomes." We subsequently apply the estimates for potential reductions in adverse health outcomes to the estimates of economic burden for these selected health outcomes that were presented in the March 26, 2004 report on "Revised Annual Costs to the U.S. from Selected Disease Burden" and supplemented in the April 6, 2004 report.

Below we present our findings for each of ten selected health outcomes – diabetes, asthma, injury/deaths from risk-taking behavior in youth (via motor vehicle accidents and violence), obesity, low birth weight, mental retardation, impaired cognitive ability (from mercury and pesticide exposure), and autism.

Although the data collection protocol for the NCS is not established yet, the exposures below were identified in the November 25, 2003 document prepared by the ICC hypotheses committee as those that capture the scope of the NCS.

- Physical environment – aspects of the physical environment that relate to child health and development such as housing quality and neighborhood and community conditions.
- Chemical exposures – Chemical environmental contaminant exposure through contact with air, water, soil, food, or industrial products such as PCBs, phthalates, pesticides, and heavy metals.
- Biologic environment – Exogenous factors such as endotoxin, viral and bacterial agents, and diet and response to those factors; physiologic mechanisms underlying relationships between in utero and early life exposures and health outcomes.
- Genetics – Examination of the interaction between genetic factors and chemical, biological, and social exposures in the expression of disease.
- Psychosocial – Assessment of the psychosocial environment.

These five categories of exposure will cover the majority of risk factors known to contribute to the selected health outcomes discussed in this report. As previously discussed in the estimates of disease burden report, for five of the health outcomes listed in Table 1 – diabetes, asthma, obesity, low birth weight, and injury – the estimated annual costs represent costs incurred in 2003 from these outcomes (i.e., yearly costs for prevalent cases). For the other outcomes – mental retardation, autism, and cognitive ability, the estimated costs represent lifetime costs for the cohort of subjects newly affected by these outcomes in a single year (i.e., lifetime costs for new incident cases).

For each selected health outcome, Table 1 summarizes our estimates of the range of potential reductions attributable to the NCS and the potential economic savings associated with those reductions. Under the discussion of each health outcome below, we consider the extent to which the known risk factors of the outcome will be studied by the NCS and consider that when estimating the potential reduction in the outcome from study findings. Of consideration when establishing these estimates were the number of research studies being conducted on these health outcomes and the current state of the science in the area. Also considered were the percent reductions in health outcomes attributable to research for similar research studies (e.g. case studies on SIDS, Cardiovascular Disease, and lead poisoning).

Table 1. Summary of Potential NCS Impact on Selected Health Outcomes

Health Outcome	Estimated Annual Economic Burden (in billions of 2003$)	Range of Potential Reductions Attributable to NCS	Potential Annual Economic Savings from NCS
Diabetes	$136.6 billion	0.5 – 1.5 %	$0.7-2.1 billion
Asthma	$14.5	3 – 7 %	$0.4–1.0 billion
Obesity (excl. diabetes)	$46.3	2 – 4 %	$0.9-1.9 billion
Low Birth Weight	$13.1	4 – 7 %	$0.5-0.9 billion
Mental Retardation	$51.2	2 – 5 %	$1.0-2.6 billion
Injuries/Deaths from Aggressive Behavior			$0.07-0.16 billion
Motor Vehicle Accidents	$19.0	0.15 – 0.35 %	$0.03–0.07 billion
Violence	$24.3	0.15 – 0.35 %	$0.04 – 0.09 billion
Impaired Cognitive Ability (1 IQ point) from:			$0.19 - 0.46 billion
Mercury Exposure	$0.8 (60,000 at-risk newborns or 1.5% of total)	5 - 15 % of at-risk newborns (3,000-9,000, 0.08-0.15% of total)	$0.04 - 0.12 billion
Nonpersistent Pesticide Exposure	$49.0 (90 percent of births)	0.3 – 0.7 %	$0.15 - 0.34 billion
Autism	$40.6	0.5 – 1.5 %	$0.2 - 0.6 billion
Total	$395.4 billion		$4.0 – 9.7 billion

Conservative Nature of Estimates

For the purpose of this cost impact analysis, we used lower estimates of reductions in the NCS selected health outcomes than those seen in the research case studies, which were:

- A 57 percent decline in SIDS rate, which we attributed to a group of research studies,
- A 40-60 percent decline in CV disease risk factors and mortality rate of which we attributed about one-third to Framingham or 13 to 20 percent, and
- An 87 percent decline in children's blood lead levels based on a series of prevention and intervention measures.

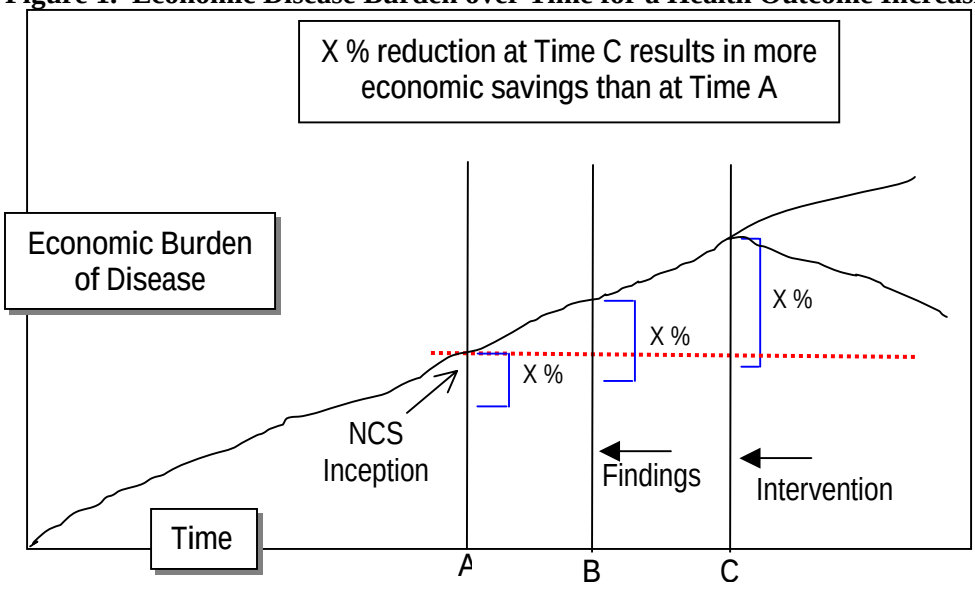
In general, we attempted to use low estimates of potential reductions in health outcomes so as not to overstate the potential gains from the study. Throughout our analyses we attempted to err on the side of being conservative. A few reasons that support this conservative philosophy include:

- It is possible that not all of the cited hypotheses will be verified. Although our selected case studies all showed positive results of research, there are other research studies that have not resulted in significant declines in their targeted health outcome.

- For many of the selected health outcomes, current medical knowledge is at a relatively high level compared to knowledge of CV disease in 1950.
- For many of the selected health outcomes, there are numerous potential risk factors. The targeted factors cited in the NCS core hypotheses represent a subset that, although important, will not be associated with all cases.
- The impact of findings associating prenatal and early childhood risk factors with health outcomes affecting both children and adults (e.g. diabetes and obesity) may take a relatively long time to reduce prevalence throughout all age groups.

Another conservative aspect of our analysis is that we calculated cost savings based on current disease burden. For health outcomes whose current trends are increasing, this methodology does not factor in potential cost savings based on a future increase in the health outcome if the research were not to be performed. Figure 1 attempts to illustrate this concept.

Figure 1. Economic Disease Burden over Time for a Health Outcome Increasing in Prevalence



1. DIABETES (TYPES 1 & 2)

Description - Diabetes mellitus is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. There are several major types of diabetes: Type 1, Type 2, Gestational, and Pre-diabetes. Type 2 diabetes is the most prevalent form of diabetes. In Type 2 diabetes, either the body does not produce enough insulin or the cells ignore the insulin. Approximately 90-95 percent of Americans who are diagnosed with diabetes have Type 2 diabetes (ADA website). Type 1 diabetes is usually diagnosed in children and young adults, and was previously known as juvenile diabetes. Type I diabetes is always insulin-dependent and therefore entails large, ongoing lifetime costs. Type II diabetes, with an average age of diagnosis greater than 45 years, can often be treated only by diet or comparatively inexpensive oral medications, thereby reducing its economic burden.

Magnitude of the Problem - CDC's National Diabetes Fact Sheet cites total prevalence of diabetes in the United States in 2002 to be 18.2 million, or 6.3% of the population – with an estimated 13 million that have been diagnosed and 5.2 million people (or nearly one-third) that are unaware that they have the disease. The prevalence of diabetes has gotten progressively worse over the last two decades. Approximately one in every 400 to 500 children/adolescents has Type 1 diabetes. As obesity increases in younger populations, more children and adolescents are being diagnosed with Type II diabetes, somewhat changing the distribution of economic costs for the disease.

Risk Factors - Type 1 and Type 2 diabetes have different causes, yet two factors are important in both: 1) an inherited predisposition to the disease and 2) an environmental trigger. Risk factors for Type 1 diabetes may include autoimmune, genetic, and environmental factors, while Type 2 diabetes is associated with older age, obesity, family history of the disease, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity (CDC, 2003).

Type 1 diabetes - In most cases of Type 1 diabetes, people inherit genetic risk factors from both parents. The American Diabetes Association (ADA) offers a listing of potential environmental triggers – including cold weather, viruses, diet, and breastfeeding. In many people, the advancement of Type 1 diabetes seems to take many years. In young children, e.g., less than 10 years, however, the onset of symptoms can be relatively sudden. In experiments that followed relatives of people with Type 1 diabetes, researchers found that most of those who later got diabetes had certain autoantibodies in their blood for years before clinical diagnosis.

Type 2 diabetes - The prevalence of Type 2 diabetes has tripled in the last 30 years, and much of the increase is due to the dramatic upsurge in obesity. Obesity is a strong risk factor for Type 2 diabetes. It should be noted that Type 2 diabetes is increasingly being diagnosed in children and adolescents, particularly in ethnic minorities (CDC, 2003).

Other Research Studies - Research studies have determined that lifestyle interventions including changes in diet and moderate-intensity physical activity can ***prevent*** or delay the onset of Type 2 diabetes among high-risk adults (at least 10 million Americans). The findings came from the Diabetes Prevention Program (DPP), a major clinical trial in 3,234 people with impaired glucose tolerance, a condition that often precedes diabetes. The DPP, conducted at 27 centers nationwide, is the ***first major trial*** to illustrate that diet and exercise can effectively delay diabetes in a diverse American population of overweight people with impaired glucose tolerance (IGT). Participants randomly assigned to intensive lifestyle intervention reduced their risk of getting Type 2 diabetes by 58 percent. Past studies have also shown that medications have been successful in preventing diabetes in some population groups. There are no known methods to ***prevent*** Type 1 diabetes, however, several clinical trials are in progress or being planned (CDC, 2003). A clinical trial funded by NIH and the Juvenile Diabetes Research Foundation is attempting to confirm preliminary studies that show pancreatic islet transplantation reduces the incidence of complications from diabetes and may potentially eliminate the need for insulin injections by Type 1 diabetes patients. Another study focused on youth, funded by CDC and NIH, is a 5-year multicenter study, SEARCH for Diabetes in Youth, to examine the current status of diabetes among children and adolescents in the United States. The SEARCH study will

investigate diabetes, especially Type 2 diabetes, as these disease rates are increasing each year in children and youth.

Potential NCS Findings and Subsequent Interventions

A number of NCS core hypotheses focus on insulin resistance, including impaired glucose metabolism during pregnancy and intrauterine growth restriction. Study findings relating these two factors to insulin resistance in offspring could potentially yield targeted interventions for populations in the highest risk categories. Because there are other ongoing research studies on diabetes risk factors, any future reductions in diabetes prevalence cannot be fully attributed to the NCS; however, if the NCS yields unique findings related to the two risk factors mentioned above (and potentially others), certainly some of any subsequent reduction would be attributable to the study. In the case of the Diabetes Prevention Program, it was determined that lifestyle interventions including changes in diet and moderate-intensity physical activity can prevent or delay the onset of Type 2 diabetes among high-risk adults. Due to the nature of this intervention, it seems likely that the SIDS study may serve as an example of how an outcome can be impacted relatively quickly by behavioral modifications.

Although in the case of SIDS suggested behavioral changes led to greater than 50 percent declines in the health outcome, behavioral modifications to prevent Type 1 diabetes may not be as easily adopted. On the other hand, the study may be able to identify other modifying environmental triggers (e.g. viral infection) and how they affect a subset of genetically predisposed people to cause diabetes. Given that the potential prevention measures would be related to prenatal and early childhood risk factors, the short-term impact would be a reduction in diabetes in young children. As these children age, this will eventually lead to a reduction in the rate of adult diabetes as well. For cost impact estimation, we make the assumption that 5 percent of diabetes cases will be impacted by potential findings related to impaired maternal glucose metabolism and intrauterine growth restriction (and other identified risk factors) that stem from the NCS. Of the five percent of impacted cases, we assume that new prevention measures will result in 20 percent of these cases not contracting diabetes for a 1 percent overall decline in current levels of diabetes.

Assumptions Enabling Estimation of NCS Economic Impact

In order to estimate the potential impact of the NCS on diabetes, we make the following assumptions:

- NCS findings associating impaired glucose metabolism during pregnancy and intrauterine growth restriction with insulin resistance will lead to targeted prevention measures and interventions in the susceptible population that can reduce the prevalence of the disease by 1 percent. For cost impact estimation, we use a range of 0.5 to 1.5 percent overall reduction.
- Total 2003 cost of diabetes is $136.6 billion

This would yield annual savings between $0.7 and $2.1 billion in 2003 dollars.

References

Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2003. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2003.

Diabetes in America, 2nd Edition Table of Contents. Available online at: http://diabetes.niddk.nih.gov/dm/pubs/america/contents.htm

American Diabetes Association online resources. Available online at: **http://www.diabetes.org/genetics.jsp** and **http://www.diabetes.org/about-diabetes.jsp**

2. ASTHMA

Description - Asthma is a chronic immunological disease that interferes with pulmonary function, resulting in repeated episodes of breathlessness, wheezing, chest tightness, and coughing. These episodes, commonly known as asthma attacks, are characterized by inflammation and swelling of the airways that carry air to the lungs. As the muscles surrounding the airways tighten, the passage of air to and from the lungs becomes increasingly difficult.[1]

Risk Factors - Several risk factors for asthma sensitization and exacerbation have been identified, the strongest of which are family history, certain allergic conditions, and repeated environmental exposures to one or more allergens. Asthma, like other chronic conditions, is a multifactorial disease. To develop asthma, a person must first be susceptible to the disease. Susceptibility is influenced by genetics, but other factors leading to asthma development are still poorly understood. Researchers have proposed several theories, citing both behavioral or lifestyle risk factors and environmental exposures as potential contributors to the onset of asthma symptoms.[2] Asthma exacerbation has also been associated with both behavioral and environmental triggers. Established environmental risk factors for asthma include house dust mites, cat dander, and cockroach allergens. Lifestyle or behavioral characteristics that have been identified as potential risk factors for asthma development and exacerbation include stress, lack of exercise, and obesity.

It has been estimated that at least 60 percent of asthma attacks are triggered by allergens in the environment.[3] Many of these allergens can be found in indoor residential environments. Dust mites, cockroaches, molds, environmental tobacco smoke, airborne pollutants (e.g. ozone, particulate matter), and pet dander have all been implicated as potential triggers for asthma symptoms. A recent study estimated that eliminating residential risk factors, if causally associated with asthma, would result in a 39 percent decline in asthma among children under 6 years old[4] and a 44 percent decline among older children and adolescents in the U.S.[5]

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[1] http://www.cdc.gov/nceh/airpollution/asthma/faqs.htm
[2] Redd, 2002
[3] Associated Press. 2004. Allergy season troubles asthma sufferers. Posted online March 31, http://www.cnn.com/2004/HEALTH/03/30/allergy.asthma.ap/.
[4] Lanphear, B.P., Aligne, C.A., Auinger, P., Weitzman, M., and R.S. Byrd. 2001. Residential exposures associated with asthma in US children. Pediatrics 107(3): 505-511.

Nevertheless, further research is needed to demonstrate a dose-response relationship between many of the environmental agents described above and asthma sensitization or exacerbation. For example, a study of 1,000 inner-city children stricken with asthma sponsored by NIH illustrated that reducing exposure to cockroaches and other insects using low-cost preventive measures can reduce the severity and frequency of asthma-related health problems.

Magnitude of the Problem - In the U.S., asthma prevalence has increased dramatically over the past 20 years.[6] Overall, the occurrence of asthma has more than doubled since 1980.[7] Among children, asthma is now the most common chronic illness, affecting over 6 million, or nearly 9 percent, of those under 18 years of age.[8] The incidence of new asthma cases is highest in children younger than 5 years of age. Childhood asthma is a disorder with genetic predispositions and a strong allergic component. Approximately 75 to 80 percent of children with asthma have significant allergies, which substantially increases susceptibility.[9]

Other Research Studies - Asthma research has focused primarily on asthma sensitization and exacerbation. Significantly more research has been conducted on the relationship between environmental exposures and asthma. NIH and CDC have funded a significant amount of asthma research. The research studies listed above highlight the fact there are already asthma-related studies in place. Despite these studies, the NCS offers the unique ability to simultaneously measure multiple risk factors for asthma, including genetic traits and individual susceptibility to specific environmental agents. It could be anticipated that as a result of the NCS, targeted interventions and prevention strategies could be established with the potential to significantly reduce the annual economic burden of asthma (from November 2002 report).

Potential NCS Findings and Subsequent Interventions

NCS Core Hypotheses 4.1 through 4.5 all relate to asthma risk factors (listed below) that could be significantly impacted with subsequent prevention and intervention methods.

- 4.1 Exposure to indoor and outdoor air pollution and bioaerosols is associated with increased risk of asthma.
- 4.2 Respiratory viral infection early in life is associated with increased risk of asthma.
- 4.3 Maternal stress during pregnancy is associated with increased risk of asthma.
- 4.4 Antioxidant constituents of diet decrease risk of asthma.
- 4.5 Early exposure to bacterial and microbial products decreases risk of asthma.

If the NCS is successful at establishing the validity of one or more of these core hypotheses, new prevention methods could be developed to lower the risk of developing asthma (such as diet guidelines for at-risk children, stress management techniques for pregnant women, and treatment methods for early childhood respiratory viral infections).

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[5] Lanphear, B.P., Kahn, R.s., Berger, O., Auinger, P., Bortnick, S.M., and R.W. Nahhas. 2001. Contribution of residential exposures to asthma in US children and adolescents. Pediatrics 107(6). (http://www.pediatrics.org/cgi/content/full/107/6/e98)

[6] Redd, S.C. 2002. Asthma in the United States: Burden and Current Theories. Environmental Health Perspectives 110(Suppl. 4): 557-560.

[7] AP, 2004

[8] http://www.cdc.gov/nchs/fastats/asthma.htm

[9] http://www.lungusa.org/asthma/merck_pediatric.html

For cost impact purposes, we assume that findings and subsequent prevention measures related to the relevant core hypotheses can lead to a 5 percent reduction in current asthma levels and annual disease burden. Our thinking in estimating this potential reduction was tempered by a number of factors including 1) the asthma-related hypotheses representing only a subset of potential asthma risk factors, 2) other research studies currently investigating asthma risk factors, and 3) the current state of knowledge regarding asthma. On the other hand, although much is known and is being investigated currently regarding asthma, asthma rates are increasing. Thus, clearly there is more to learn regarding asthma risk factors. Although the impact from the NCS may not be as large as that attributable to the Framingham Study (13-20 percent) because of the tempering factors, we think a 5 percent reduction is a reasonable estimate.

Assumptions Enabling Estimation of NCS Economic Impact

In order to estimate the potential impact of the NCS on asthma, we make the following assumptions:

- NCS findings will lead to the development of targeted interventions and primary prevention strategies related to maternal stress during pregnancy, antioxidants in the diet, early childhood respiratory viral infections, and other identified risk factors, which will reduce the incidence and severity of the disease by five percent (from the current level).
- We estimate a reduction of 3 to 7 percent to estimate the NCS cost impact.
- Total 2003 cost of asthma is $14.5 billion

These assumptions would enable economic savings of $0.4-1.0 billion each year.

3. OBESITY

Description - Overweight and obesity are a result of energy imbalance over a long period of time. Most experts find that while no single factor accounts for the increasing number of overweight and obese adults, increased caloric intake and decreased physical activity are major contributors to the current obesity epidemic. Overweight and obesity are known risk factors for diabetes, heart disease, stroke, and some forms of cancer. Furthermore, obesity can be a precursor of high cholesterol, complications during pregnancy, psychological disorders, and increased surgical risk. An overweight adult is defined as one with a body mass index (BMI) between 25 and 29.9, while an obese adult has a BMI of 30 or higher. There is no generally accepted definition for obesity for children and adolescents, however overweight is defined for children and adolescents as a sex-and-age specific BMI at or above the 95th percentile, based on revised growth charts by the CDC.

Magnitude of the Problem - The prevalence of obesity has increased substantially over the last two decades, while overweight among adolescents has tripled. According to data from the 1999-2000 NHANES, an estimated 31 percent of U.S. adults aged 20 years and older — nearly 59 million people — were obese.[10] [Note that 31 percent of persons >19 years old from U.S. Census Bureau 2003 population estimates yields approximately 65 million. Thus, even if obesity rates stayed level, costs may have increased by about 10 percent from population growth.] The

[10] CDC Website. Page last updated on 3/1/04. Last accessed on 4/2/04. Available online: http://www.cdc.gov/nccdphp/dnpa/obesity/economic_consequences.htm

prevalence of overweight is increasing for U.S. children and adolescents. Approximately 10.4 percent of 2 to 5 year olds, 15.3 percent of children ages 6 to 11, and 15.5 percent of adolescents ages 12 to19 were overweight in 2000.

Risk Factors - The cause of energy imbalance for each individual may be due to a combination of several factors such as individual behaviors, environmental factors, and genetics. The November 2002 report stated that 50 genes associated with obesity have been located in the human gene map; however, genes do not always predict future health. Genes and behavior may both be a necessary presence for an increased risk of overweight or obesity. In some cases multiple genes may increase one's susceptibility for obesity and require outside factors; such as abundant food supply or little physical activity, both of which are influenced by social, economic, and physical environments.[11]

Other Research Studies - Reasonably little is known about the prevention and treatment of obesity on a population-wide basis.[12] According to a survey conducted by Ogden et al. (2002), the prevalence of overweight among children in the U.S. is continuing to increase, especially among Mexican-American and non-Hispanic black adolescents. From this study, it is not clear what interventions will work to effectively reduce the high prevalence of overweight among youth; however, interventions may focus on behavior of parents, who determine their children's diet and physical activity. The article also cited school-based programs to aid in diet changes or diminish sedentary behaviors. Additional research will need to focus on reasons for the increase and interventions to reduce the prevalence.

As described above there is research in place investigating factors that may contribute to obesity, however to date, there is no single study that combines data from the prenatal period with early feeding and childhood and adolescent growth information (from November 2002 NCS report) therefore the NCS could have a major impact on this health outcome. The NCS will focus on identifying modifiable factors that account for increases in obesity and its complications over the past four decades. Given that the increase in obesity cannot be explained by genetic conditions alone, it is anticipated the NCS will contribute evidence regarding physical and social factors (that account for increase in prevalence and its complications) for this health outcome (from Nov 2002 NCS report). Improved knowledge of how these factors interact with genetic disposition could lead the way to the development of more targeted and effective interventions.

Potential NCS Findings and Subsequent Interventions

NCS Core Hypotheses 5.1 through 5.7 all focus on risk factors for obesity - impaired maternal glucose metabolism during pregnancy, intrauterine growth restriction, breast milk feeding compared with infant formula feeding, and dietary predictors. Potential findings linking these risk factors to obesity could lead to medical interventions and prevention measures by physicians during pregnancy to decrease the risk of impaired glucose metabolism and intrauterine growth restriction, as well as to promote targeted interventions (e.g. breast milk feeding compared with infant formula feeding) and to develop guidance enabling at-risk populations to avoid other environmental triggers that might be identified through the NCS. Because potential prevention and intervention measures may be incorporated by physicians into treatment of pregnant women,

[11] Ogden et al., 2002

[12] Flegal, KM, Carroll, MD, Ogden, CL, and Johnson, CL., JAMA, October 9, 2002 (288) 14: 1723-1727

we theorize that they could result in widespread adoption and successful reduction in subsequent cases of obesity. In the short-term, the nature of the findings and potential interventions may lead to a decline in the childhood rate of overweight; however, in the long-term, these lower childhood overweight rates could result in reduced adult prevalence of obesity as well. The effect on economic burden will increase as the impact on adult prevalence increases.

Because of the large number of environmental factors that have already been associated with obesity (e.g. behavioral factors that affect development of dietary preferences and physical activity patterns early in childhood), we assume that the NCS findings related to the prenatal and early childhood risk factors cited in the core hypotheses (impaired maternal glucose metabolism during pregnancy, intrauterine growth restriction, breast milk feeding, and dietary predictors) might only impact 25 percent of obesity cases. We also assume that a 10 percent reduction in obesity will be attributable to the NCS findings and subsequent prevention efforts based on those findings yielding a 2.5 percent overall reduction.

Because the Framingham Study led to findings related to heart disease risk factors responsible for approximately 13 to 20 percent declines in certain risk factors and heart disease mortality, we thought an estimate of 10 percent that is a bit below that lower bound would be reasonable. Because much is still unknown about the prevention and treatment of obesity on a population-wide basis, there is opportunity for reduction; however, although prenatal prevention measures may be more easily implemented, it is more difficult to achieve widespread implementation of other prevention measures related to behavior and diet.

Assumptions Enabling Estimation of NCS Economic Impact

In order to estimate the potential impact of the NCS on obesity (excluding diabetes), we make the following assumptions:

- NCS findings related to impaired maternal glucose metabolism and intrauterine growth restriction can lead to the development of targeted interventions and primary prevention strategies.
- NCS findings related to these risk factors will impact 25 percent of obesity cases.
- Targeted prevention measures developed based on NCS findings will reduce obesity by 10 percent in these in-scope cases for a total reduction of 2.5 percent. We use a range of 2 to 4 percent for the cost impact estimates.
- Total 2003 cost of obesity (excluding diabetes) is $46.3 billion.

These assumptions would enable economic savings in the range of $0.9 to $1.9 billion each year.

4. LOW BIRTH WEIGHT

Description - Low birth weight (LBW) is defined as a weight of less than 5 pounds, 8 ounces (2500 g) at birth. Very low birth weight (VLBW) infants weigh less than 3 pounds, 5 ounces (1500 g). In the U.S., preterm delivery (prior to the 37th week of gestation) is a primary determinant of LBW.[13] VLBW infants are predisposed to various neurodevelopmental disorders and poor health in later years. Foremost among the major handicaps common to LBW infants is

[13] Paneth, N.S. 1995. The problem of low birth weight. The Future of Children 5(1): 19-34.

cerebral palsy, which occurs about 25 times more frequently in children who had been VLBW infants compared to those weighing more than 5 pounds at birth.[14] Other conditions hypothesized with LBW infants include blindness, epilepsy, deafness, chronic lung disease, intestinal disorders, learning disabilities, and attention deficit disorder, although many of these occur with very low incidence.[15,16]

Magnitude of the Problem **-** Over 60 percent of LBW infants are born prematurely.[17] The rate of LBW in the U.S. increased steadily from 6.7% in 1984 to 7.6% in 1998, where it has remained unchanged through 2001.[18] The rate of VLBW, measured at 1.43% in both 2000 and 2001, rose moderately through the 1980s and 1990s, from 1.15% in 1980 to 1.45% in 1999.[19] LBW plays a significant role in both infant mortality and long-term disabilities. In 2000, 66 percent of all infant deaths in the U.S. were LBW.[20]

Known Risk Factors **-** Fetal defects resulting from genetic conditions or environmental exposures may hinder normal development. Medical problems of the mother, such as high blood pressure, organ problems, or certain infections, may also influence birth weight.[21] To date, three major risk factors have been associated with low birth weight: cigarette smoking during pregnancy, low pre-pregnancy weight, and low maternal weight gain. These factors account for nearly 2/3 of growth-retarded infants.[22] Drug and alcohol use also impede fetal growth.[23] Research on the incidence of low birth weight and preterm birth has uncovered significant ethnic differences in these outcomes not fully explained by lifestyle differences, variations in medical conditions between the ethnic groups, or demographic characteristics.[24] Additional research on this phenomenon might shed more light on the underlying causes of LBW.

Other Research Studies **-** Additional research is needed to identify the risk factors for low birth weight and develop effective prevention strategies. NIH has undertaken a wide range of perinatal research initiatives. Research being conducted at NIH focuses on topics such as fetal maturation, prematurity and labor inducement, and intrauterine growth retardation.[25] In 2003, the March of Dimes launched a national campaign to raise awareness and decrease rates of premature birth in the U.S. This campaign will invest $75 million over its five-year duration and raise additional funding to support research into the causes and potential treatment of prematurity.[26]

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[14] http://www.nemours.org/no/faq/faq1755.html
[15] Paneth, 1995.
[16] March of Dimes, 2004.
[17] March of Dimes, 2004.
[18] MacDorman, M.F., Minino, A.M., Strobino, D.M., and Guyer, B. 2002. Annual summary of vital statistics – 2001. Pediatrics 110(6): 1037-1052.
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[23] March of Dimes, 2004.
[24] Shiono and Behrman, 1995.
[25] http://raceandhealth.hhs.gov/3rdpgblue/infant/red.htm
[26] http://www.marchofdimes.com/aboutus/791_6775.asp

Potential NCS Findings and Subsequent Interventions

The NCS may only be able to have a limited impact on the 2/3 of LBW cases (5.1 of 7.6 cases per 100 live births) caused by known risk factors given that risk factors such as smoking during pregnancy are known and measures are being taken such as the March of Dimes campaign to raise awareness of these known risk factors (although they have not resulted in a decline in the rate of LBW yet). Although in the case of SIDS suggested behavioral changes has led to greater than 50 percent declines in the health outcome, behavioral modifications to prevent LBW appear not to be as easily adopted. On the other hand, the study may be able to identify other modifying environmental or genetic factors that interact with these known risk factors to increase risk of LBW. These findings potentially would yield targeted interventions for populations in the highest risk categories. It might be reasonable to estimate that findings on modifying environmental factors could lead to a five percent reduction in LBW cases for this group (3.3 percent of total).

For the other 1/3 of LBW cases (2.5 of 7.6 cases per 100 live births) outside the group caused by known behavioral risk factors, the NCS has potential to identify the additional risk factors that could lead to a decline in LBW among this group. As stated in NCS Core Hypothesis 1.2, the primary potential risk factor explored will be "intrauterine exposure to mediators of inflammation due to infection of either vaginal, cervical or uterine sites, or of more distal sites (e.g. periodontal disease)."

Not all of this 1/3 will be in-scope given that some of the increase in LBW is a result of "increases in preterm delivery, changes in obstetrical practices, and induction of labor" and "increases in multiple births from assisted reproductive therapies."[27] The rate of LBW was steady from 1980-1986 at 6.8 percent of live births. To be conservative, we assume that the .8 case increase from 1987-2000 was entirely attributable to the obstetrical and reproductive therapy changes. This leaves 1.7 percent of live births or 22 percent of all LBW cases that could potentially be reduced from findings associating intrauterine exposures to mediators of inflammation with increased risk of preterm birth.

In the example of the Framingham Heart Study, we saw that findings related to newly-identified risk factors helped lead to declines ranging from approximately 13 to 20 percent in various risk factors and mortality from heart disease attributable to the study. Again using an estimate slightly below that lower bound, we estimate that the NCS might be able reduce LBW by 10 percent for 1/6 of LBW cases (1.67 percent of total). We assume that a 10 percent reduction is possible based on the assumption that prevention/intervention measures could be developed that would lower the incidence of infection causing preterm birth.

Assumptions Enabling Estimation of NCS Economic Impact

In order to estimate the potential economic impact of the NCS on LBW, we make the following assumptions:

- The NCS will study the major exposures that are risk factors for LBW.

[27] Iyasu S, Tomashek K, and Barfield W. Infant Mortality and Low Birth Weight Among Black and White Infants --- United States, 1980—2000. MMWR July 12, 2002/51(27); 589-592. CDC. (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5127a1.htm)

- NCS findings associating LBW with prenatal infection can lead to the subsequent development of targeted interventions aimed at decreasing pre-term birth and subsequent morbidity and mortality.
- Total 2003 cost of LBW is $13.1 billion.
- Two-thirds of LBW cases stem from known behavior risk factors. NCS findings regarding modifying environmental factors could reduce lead to a 5 percent reduction of these cases (3.3 percent of total).
- 11 percent of LBW cases are out-of-scope because they are related to changes in obstetrical and reproductive therapy practices.
- Of the remaining 22 percent of LBW cases, findings relating intrauterine exposures to mediators of inflammation with increased risk of preterm birth or other preconception or prenatal findings of the NCS may reduce this group of cases by 10 percent (2.2 percent of total).
- Based on NCS findings, we estimate a 5.5 percent reduction in LBW. We apply a range of 4 to 7 percent in estimating potential cost savings.

These assumptions would enable economic savings in the range of $0.5 to $0.9 billion each year.

5. MENTAL RETARDATION

Description - Mental retardation (MR) is the most common developmental disorder in the U.S. This condition is characterized by lower than normal intellectual functioning and limited adaptive abilities.[28] Three criteria are typically used to diagnose MR: an intellectual functioning (IQ) level below 70-75; significant limitations in two or more adaptive skill areas; and the existence of the condition since childhood (defined as age 18 or less).[29]

Magnitude of the Problem – Mental retardation occurs in approximately 1 percent of the population. CDC's MADDSP study found that, on average from 1991-1994, about 1 percent of children ages 3-10 years had MR. The study also found that mental retardation was more common in older children (ages 6-10 years) than in younger children (ages 3-5 years). MR was also more common in boys than in girls, and more common in black children than in white children. The advocacy group The Arc reports on their website that approximately 87 percent of mental retardation cases are mildly affected while the other 13 percent are seriously limited with IQs under 50.

Risk Factors – CDC's National Center on Birth Defects and Developmental Disabilities website cites a 1992 study that identified over 350 causes of MR (http://www.cdc.gov/ncbddd/mrawareness/default.htm) including "genetic conditions, errors of metabolism, maternal environmental influences, intrauterine disorders, injury, infections," and others. The most common risk factors are genetic conditions and complications during

[28] [Anonymous]. 2002. JAMA Patient Page: Mental Retardation. Journal of the American Medical Association 288: 1548.
[29] American Association on Mental Retardation. 1992. *Mental Retardation: Definition, Classification, and Systems of Supports, 9th Edition*. Washington, DC.

pregnancy and during birth.[30] Expectant mothers who develop infections like rubella during pregnancy can increase the risk of delivering a baby with MR. Some post-conception triggers of mental retardation can be avoided (e.g. drinking alcohol). Complications during labor and after birth (e.g., inadequate oxygen supply to the baby, extreme malnutrition, and physical trauma) can also result in mental retardation. Health problems contributing to MR may occur at any point in a child's development. Diseases such as the measles, meningitis, and whooping cough have been linked to MR, as have conditions associated with prolonged or even short term high fevers. Certain health problems leading to MR (e.g. serious head injury and exposure to poisons such as lead and mercury) can be avoided with proper preventive steps.[31] The American Association of Mental Retardation reported that as many as *50 percent of mental retardation cases have been found to possess more than one causal factor*. For many cases, no cause is identified. The Arc cites a 1993 report by Kozma and Stock estimating that *75 percent of mild MR cases have unknown cause*.

Other Research Studies - CDC conducts and supports programs to prevent mental retardation from occurring and to improve the health and quality of life for people who are affected. One ongoing study of interest, the Metropolitan Atlanta Developmental Disabilities Study (MADDS), was the first U.S. population-based epidemiologic study of the prevalence of mental retardation, cerebral palsy, hearing loss, vision impairment, and epilepsy among children 10 years of age. The success of MADDS prompted CDC to establish the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP) in 1991, an ongoing system for monitoring the occurrence of selected developmental disabilities. CDC is tracking the number of children with mental retardation in a five-county area in metropolitan Atlanta, Georgia.

Potential NCS Findings and Subsequent Interventions - A number of NCS hypotheses focus on risk factors associated with mental retardation – impaired metabolism during pregnancy, intrauterine disorders and infection, and repeated head trauma. Measures of these factors have the potential to enable findings related to mental retardation. Potential findings linking these and other risk factors to mental retardation could lead to medical interventions and prevention measures by physicians during pregnancy to decrease the risk of infections and impaired metabolism, as well as to development of guidance enabling at-risk populations to avoid other environmental triggers that might be identified through the research. Because potential prevention and intervention measures may be incorporated by physicians into treatment of pregnant women, we theorize that they could result in widespread adoption and successful reduction in cases of mental retardation.

Regarding the portion of MR cases that might be affected by NCS findings, we assume that half of the severe MR cases (13 percent of total) and 75 percent of the mild MR cases (87 percent of total) have potential to be impacted by the NCS research findings – for a total of 72 percent of all cases. We did not find any references citing percent of cases caused by inherited genetic disorders, so to be conservative we excluded half of the severe cases and a quarter of the mild cases.

[30] NDCCD, 2004.
[31] NDCCD, 2004.

Because of the large number of causes that have been identified, we assume that the NCS findings related to the risk factors mentioned above (impaired metabolism, intrauterine disorders, etc.) might only lead to a five percent reduction in the 72 percent of in-scope cases. Much is still unknown about the causes of MR, thus, the potential for a positive impact exists. Because we are not sure what percentage of cases might be affected by the core hypotheses, however, we use the conservative estimate of a 5 percent reduction.

Assumptions Enabling Estimation of NCS Economic Impact

In order to estimate the potential impact of the NCS on mental retardation, we make the following assumptions:

- The NCS will study the major types of exposures that are risk factors for mental retardation.
- NCS findings can lead to the development of primary prevention measures that can reduce certain behavioral and environmental risk factors of mental retardation.
- Half of severe MR cases (13 percent of total) are in-scope.
- 75 percent of non-severe MR cases (87 percent of total) are in-scope for impact by NCS findings.
- Total 2003 cost of mental retardation is $51.2 billion.
- Of the 72 percent of all MR cases deemed in-scope, we assume a 5 percent reduction which results in an estimated 3.6 percent reduction in total MR cases. We apply a range of 2 to 5 percent to develop estimates of cost reduction.

These assumptions would enable estimated economic savings in the range of $1.0-2.6 billion each year.

6. INJURIES/DEATHS FROM RISK-TAKING BEHAVIOR IN CHILDHOOD AND ADOLESCENTS: MOTOR VEHICLE ACCIDENTS

Description – The January 24, 2004 "New Unintentional Injury Hypothesis" states that "it is known that risk of injury during childhood and adolescence is associated with risk-taking behavior. We hypothesize that risk taking behavior in children and adolescents is related to the biological reactivity of the individual in infancy, and that this reactivity is modified during development by parent rearing styles and the physical context in which the child is raised. Moreover, we postulate that the biological reactivity related to risk taking is affected by polymorphisms in genes controlling serotonin metabolism. Physical and social (parenting etc.) environments affect the risk of injuries differentially according to biologically determined reactivity (genetic polymorphisms for serotonin metabolism)." We theorize that potential outcomes of this risk-taking behavior are both motor vehicle accidents (MVAs) and violence.

Magnitude of the Problem – Teenagers represented 10 percent of the U.S. population in 2000 yet accounted for 14 percent of all motor vehicle–related deaths (IIHS 2003).[32] In 2002, 3,827 drivers 15 to 20 years old were killed, and an additional 324,000 drivers were injured in motor vehicle crashes. Motor vehicle crashes are the leading cause of death for 15 to 20 year olds.[33]

[32] http://www.iihs.org/safety_facts/fatality_facts/teens.htm
[33] http://www-nrd.nhtsa.dot.gov/pdf/nrd-30/NCSA/TSF2002/2002ydrfacts.pdf

The National Highway Traffic Safety Administration (NHTSA) reports that 14 percent of fatal traffic accidents (in 2002) involved drivers 15-20 years old (although that population only accounted for 6.6 percent of drivers). CDC cites aggressive driving being associated with 1/3 of traffic crashes and 2/3 of fatal crashes. Another report cites risky driving behaviors being common among young people.

Risk Factors – Aggressive behavior by adolescents has been implicated as a cause of injury and death from motor-vehicle accidents.

Other Research Studies – CDC conducts and sponsors research to develop practical, community-based prevention strategies for motor vehicle–related injuries, and has been instrumental in framing motor vehicle injury as a public health problem and in helping to raise public awareness that these injuries are predictable and preventable, part of which focuses on teen drivers. For example, CDC's Youth Risk Behavior Survey tracks motor vehicle injury risk behaviors among teenagers. Another CDC study in Gwinnett County, Georgia studied driving behaviors among local teens to identify potentially modifiable risk factors and found that three behaviors were associated with increased risk for motor vehicle crashes: driving 20 mph over the speed limit, passing a car in a no-passing zone, and taking risks while driving in traffic because it makes driving more fun.

Potential NCS Findings and Subsequent Interventions

The January 25, 2004 NCS hypothesis on unintentional injury theorizes that genetic polymorphisms for serotonin metabolism affect the biological reactivity related to risk taking. If the NCS is able to validate this hypothesis or identify other factors related to risk-taking behavior, it could lead to prevention measures such as new parenting guidance for those most at-risk. Although parenting changes and moderating children's behavior is not as easy to implement when compared to behavioral modifications suggested by SIDS research, the guidance may be able to reduce certain risk-taking behavior and aggressive behavior that could reduce the number of MVAs involving young drivers.

Although we are not sure what percentage of the population might be affected the findings of the core hypothesis related to polymorphism-related aggressive behavior, for purposes of this cost-impact analysis we estimate that 5 percent of the population involved in youth MVAs will be impacted by the findings enabled by the NCS. Because of the potential difficulty in implementing parenting styles and shaping children's behavior, we further assume that prevention measures will only be able to reduce injuries from MVAs by 5 percent. This combination would result in a 0.25 percent reduction in cost of youth MVAs.

Assumptions Enabling Estimation of NCS Economic Impact

In order to estimate the potential impact of the NCS on reducing motor vehicle accidents caused by aggressive driving by 15-20 year olds, we make the following assumptions:

- NCS findings associating genetic polymorphisms for serotonin metabolism and risk-taking behavior for certain parenting styles can lead to the reduction of certain behavioral and environmental risk factors of aggressive behavior.
- NCS findings on polymorphism-related risk-taking behavior will impact 5 percent of the population involved in youth MVAs.

- Subsequently developed prevention measures will lead to reduction in injuries/deaths from MVAs involving 15-20 year olds by 5 percent. A range of 3 to 7 percent is used for the cost impact analysis for cost reductions of 0.15 to 0.35 percent.
- Total estimated 2003 cost of injuries from MVAs in 15-20 year olds is $19.0 billion.

These assumptions would enable estimated economic savings in the range of $29 to $67 million each year.

7. INJURIES/DEATHS FROM RISK-TAKING BEHAVIOR IN CHILDHOOD AND ADOLESCENTS: VIOLENCE

Description – The January 24, 2004 "New Unintentional Injury Hypothesis" states that "it is known that risk of injury during childhood and adolescence is associated with risk-taking behavior. We hypothesize that risk taking behavior in children and adolescents is related to the biological reactivity of the individual in infancy, and that this reactivity is modified during development by parent rearing styles and the physical context in which the child is raised. Moreover, we postulate that the biological reactivity related to risk taking is affected by polymorphisms in genes controlling serotonin metabolism. Physical and social (parenting etc.) environments affect the risk of injuries differentially according to biologically determined reactivity (genetic polymorphisms for serotonin metabolism)." We theorize that potential outcomes of this risk-taking behavior are both motor vehicle accidents (MVAs) and violence.

Magnitude of the Problem – The U.S. Department of Justice cites that 21 percent of all personal crimes of violence committed in 2002 involved a single-offender 15-20 years old. This includes completed acts of violence as well as attempted/threatened violence.[34] A 2001 report by Miller et al. estimated that juveniles were 25 percent of both the victims and perpetrators of violent crimes committed in Pennsylvania in 1993.[35] A 1996 report by Miller et al. estimated that the victim costs of violent crime in the United States to be $426 billion annually, with approximately $83 billion in tangible costs (e.g. medical bills, lost earnings), plus $343 billion in intangible losses (e.g. pain, suffering, reduced quality of life). Excluded in these totals were criminal justice costs associated with incarcerating offenders. For purposes of this cost impact analysis, we will focus on the tangible costs only to be consistent with the burden estimate used for the other health outcomes. Inflating the $83 billion estimate to 2003$ using the CPI ($83B x 1.1727) results in $97.3 billion in tangible costs. If we assume that 25 percent of the costs are associated with juveniles, we obtain an estimate of $24.3 billion in 2003.

Risk Factors – Risk and protective factors exist in every facet of life - individual, family, school, peer group, and community. Individual characteristics interact in complex ways with people and conditions in the environment to produce violent behavior. The strongest risk factors during childhood are involvement in serious but not necessarily violent criminal behavior, substance use, being male, physical aggression, low family socioeconomic status or poverty and antisocial parents - all individual or family attributes or conditions.[36] Serious violence is part of a lifestyle

[34] http://www.ojp.usdoj.gov/bjs/pub/pdf/cvus/current/cv0239.pdf
[35] Miller TR, Fisher DA, and Cohen MA. Costs of Juvenile Violence: Policy Implications. Pediatrics Vol. 107 No. 1, January 2001.
[36] http://www.surgeongeneral.gov/library/youthviolence/chapter1/sec3.html#chapter4

that includes drugs, guns, precocious sex, and other risky behaviors. Youths involved in serious violence often commit many other types of crimes and exhibit other problem behaviors, presenting a serious challenge to intervention efforts. Successful interventions must confront not only the violent behavior of these young people, but also their lifestyles, which are teeming with risk.

Other Research Studies – Much of what is known about the onset, prevalence, and other characteristics of serious violence during the adolescent years comes from four important longitudinal surveys, only one which is nationally representative, the National Youth Survey (NYS). Longitudinal research has enabled investigators to describe the emergence of violence in terms of two life-course trajectories. In the early-onset trajectory, violence begins before puberty, while in the late-onset trajectory it begins after puberty, at about age 13. These two trajectories suggest insights into the likely course, severity, and duration of violence over the life span and have practical implications for the timing of intervention programs and strategies. Other research has examined the co-occurrence of serious violence and other problems, including drug use and mental disorders, and some has looked at factors associated with the end of youth violence or its continuation into adulthood. Both of these areas warrant more study.[37] Research also demonstrates that prevention programs and strategies can be effective against both early- and late-onset forms of violence in general populations of youths, high-risk youths, and even youths who are already violent or seriously delinquent. Despite these positive findings, current research on youth violence prevention has important limitations. For example, relatively little is known about the scientific effectiveness of hundreds of youth violence programs currently in use in schools and communities in the United States.

Potential NCS Findings and Subsequent Interventions

The January 25, 2004 NCS hypothesis on unintentional injury theorizes that genetic polymorphisms for serotonin metabolism affect the biological reactivity related to risk taking. If the NCS is able to prove this hypothesis, it could lead to prevention measures such as new parenting guidance for those most at-risk. Although parenting changes and moderating children's behavior is not as easy to implement when compared to behavioral modifications suggested by SIDS research, the guidance may be able to reduce certain risk-taking behavior and aggressive behavior that could reduce the number of violent crimes committed by young people.

Although we are not sure what percentage of the population might be affected the findings of the core hypothesis related to polymorphism-related aggressive behavior, for purposes of this cost-impact analysis we estimate that 5 percent of the population involved in juvenile violence will be impacted by the findings enabled by the NCS (which is consistent with our estimate for MVAs). For the same reasons cited in the MVA section (potential difficulty in implementing parenting styles and shaping children's behavior), we further assume that prevention measures will only be able to reduce juvenile violence by 5 percent. This combination would result in a 0.25 percent reduction in victim's cost of juvenile violence.

Assumptions Enabling Estimation of NCS Economic Impact

In order to estimate the potential impact of the NCS on reducing violent crimes by youth, we make the following assumptions:

[37] http://www.surgeongeneral.gov/library/youthviolence/summary.htm (chapter 2 has prevalence info)

- NCS findings associating genetic polymorphisms for serotonin metabolism and risk-taking behavior for certain parenting styles can lead to the reduction of certain behavioral and environmental risk factors of aggressive and violent behavior.
- NCS findings on polymorphism-related risk-taking behavior will impact 5 percent of the population involved in juvenile violence.
- Adoption of prevention measures based on NCS findings will lead to a 5 percent reduction in violence among young people. A range of 3 to 7 percent is used for the cost impact analysis for overall cost reductions of 0.15 to 0.35 percent.
- Estimated tangible victim related costs of violence were $97.3 billion in 2003$ (inflated from $83 billion in 1996 using the CPI). [Note that these costs are conservative in that they do not include costs of incarceration or social programs related to the perpetrators of violent crime.]
- Juvenile violence composes 25 percent of all violent crimes.
- Total estimated 2003 victim's cost of violence for youth less than 20 years old is $24.3 billion.

These assumptions would enable estimated economic savings in the range of $37 to 85 million each year.

8. IMPAIRED COGNITIVE ABILITY FROM MERCURY EXPOSURE (OR OTHER NON-PESTICIDE UBIQUITOUS NEUROTOXINS)

Description - Mercury is a highly toxic element that is found both naturally and as an introduced contaminant in the environment. Different forms of mercury can have differing health effects depending on what form the mercury is in and the route of exposure. Of greatest concern is the most toxic form of mercury, methylmercury, which affects the immune system, alters genetic and enzyme systems, and can harm the nervous system. Elemental mercury, the form released from broken thermometers, can cause adverse responses when vapors are inhaled over a long period of time. Less toxic than methylmercury, elemental mercury may be found in higher concentrations in environments such as gold mine sites.[38]

Magnitude of the Problem – In 2000, the National Academy of Sciences (NAS) published a comprehensive assessment on methylmercury that estimated that more than 60,000 children are born at risk for neurodevelopmental problems associated with in utero methylmercury exposure each year. Other populations at risk include adults that consume large amounts of fish that are contaminated by mercury. Using NHANES data, Mahaffey et al. estimated that 300,000 or more newborns a year are at increased risk of in utero exposure to harmful levels of methylmercury.

Risk Factors – People are exposed to methylmercury almost entirely by consuming contaminated fish and seafood. Larger fish generally accumulate higher levels of methylmercury. People are also at risk from exposure to or inhalation of vapors from spilled mercury.

Other Research Studies – Data on adult female participants of the 1999-2000 NHANES were used to estimate the effects of dietary mercury intake on methyl mercury concentrations in the

[38] http://www.usgs.gov/themes/factsheet/146-00/

blood. Researchers analyzed whole blood samples of the NHANES participants and mercury intake data obtained from survey and dietary recall information regarding fish consumption.[39] Based on results of this analysis and the assumption that a 1:1 ratio exists between cord blood mercury concentrations and maternal blood mercury concentrations, researchers estimated that more than 300,000 newborns per year may be at increased risk of adverse neurological and developmental effects due to *in utero* exposure to methyl mercury. However, citing recent evidence that mercury concentrations are, on average, 70 percent higher in cord blood than in maternal blood, the same researchers hypothesized that as many as 630,000 infants born each year may have blood mercury levels in excess of what EPA considers to be safe.[40]

Potential NCS Findings and Subsequent Interventions

Pursuit of current NCS Hypothesis 3.1, "exposures early in life that lead to neurotoxic effects are associated with increased risk of injury," would provide information on fish consumption and mercury levels in mothers and children that, coupled with cognitive and neurological testing performed for hypotheses related to neurodevelopment, may enable identification of neurodevelopmental effects of mercury and environmental risk factors associated with these effects. Outside of reducing mercury emissions into the environment, subsequent prevention measures might entail increasing prevention measures for targeted populations of pregnant women and breastfeeding mothers most at risk for the identified effects.

Regarding the extent of any prevention efforts on health outcomes related to mercury exposure, since we could not locate references citing specific associations between mercury levels and health outcomes, we assumed that 10 percent of the population of the 60,000 at-risk newborns cited by the NAS study could be impacted by the NCS findings, resulting in an average 1 IQ point increase for that population. Note that the estimate of 60,000 at-risk newborns from the NAS study is conservative given the more recent estimate of 300,000 based on NHANES data. We utilize the estimated relationships between IQ and earnings published by Grosse et al. in 2002 to estimate the economic impact of a 1 IQ point gain in the affected population. Also note that Grosse et al. estimated the relationship between lead and IQ points at .185 to .323 IQ points per 1 µg/dL of blood lead.[41]

For a number of reasons – including the unknown relationships between mercury and IQ and the fact that there is already guidance issued regarding consumption of certain types of fish – we think it best to be conservative with the estimate of the NCS's impact on limited cognitive ability from mercury exposure. On the other hand, the NCS also presents the opportunity to discover other ubiquitous chemicals that act as neurotoxins and negatively impact cognitive ability. Thus, although the impacts felt from findings related to mercury are constrained because of the current state of knowledge about its negative effect, this estimate may be viewed as low when considering the additional opportunities for findings related to other potentially harmful chemicals.

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[39] Schober, S.E., Sinks. T.H., Jones, R.L., Bolger, P.M., McDowell, M., Osterloh, J., Garrett, E.S., Canady, R.A., Dillon, C.F., Sun, Y., Joseph, C.B., and K.R. Mahaffey. 2003. Blood mercury levels in US children and women of childbearing age, 1999-2000. Journal of the American Medical Association 289(13): 1667-1674.

[40] Mahaffey K.R., Clickner R.P., and C.C. Bodurow. 2004. Blood organic mercury and dietary mercury intake: national health and nutrition examination survey, 1999 and 2000. Environ Health Perspect. 112(5):562-70.

[41] Grosse, SD, Matte, TD, Schwartz, J, Jackson, RJ. Economic gains resulting from the reduction in children's exposure to lead in the United States. Environ Health Perspect 110:563-569 (2002).

Assumptions Enabling Estimation of NCS Economic Impact

In order to estimate the potential impact of the NCS on impaired cognitive ability from mercury exposure, we make the following assumptions:

- The NCS will study the major types of exposures that are risk factors for mercury exposure.
- NCS findings can lead to further guidance regarding avoiding mercury exposure during pregnancy and while breastfeeding.
- 60,000 newborns annually are at-risk of in-utero and early childhood mercury exposure.
- NCS findings will impact 10 percent (6,000 births) of at-risk live births each year, or 0.15 percent of annual births. We will use a range of 5 to 15 percent for developing cost impact estimates (3,000 to 9,000 births).
- The IQ-earnings slope is 1.76, i.e. a 1 IQ point increase leads to a 1.76 percent increase in lifetime earnings. This slope is the conservative estimate from Grosse et al., who used 2.0 as their base case.
- Total estimated lifetime cost of a 1 IQ point gain for 3,000 to 9,000 newborns born in 2003 is $40 to $122 million.

9. IMPAIRED COGNITIVE ABILITY FROM NONPERSISTENT PESTICIDE EXPOSURE

Description – Residential and agricultural pesticide use is widespread in the U.S., with approximately 1 billion pounds used annually.[42] Organophosphate (OP) pesticides are the most widely used insecticides available today.[43] They are referred to as nonpersistent pesticides because they break down fairly rapidly in the environment (within days or weeks), reducing their potential to accumulate in the tissues of plants, animals, or humans.

Magnitude of the Problem – OPs are considered the most likely pesticides to cause acute poisoning. From 1993 to 1996, nearly 63,000 reports were made to U.S. poison control centers about unintentional residential exposures to OPs. Almost 25,000 of these incidents involved children under 6, who are particularly vulnerable to organophosphate poisoning, and at least 482 resulted in hospitalization.[44] The NCS hypothesis report cited NHANES data indicating 90 percent of respondents with at least three metabolites of OP insecticides in their blood or urine. Studies have found that home environments throughout the U.S. are commonly contaminated with pesticides, including OP insecticides. The Minnesota Children's Pesticide Exposure Study, part of the National Human Exposure Assessment Survey (NHEXAS), monitored children between 3 and 13 years of age for exposure to pesticides. Chlorpyrifos, a commonly-used pesticide, was detected in 93 percent of the samples.[45] Other studies cited by Bradman et al.

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[42] Bradman et al., Environ Health Perspect. 2003 Nov;111(14):1779-82. (http://ehp.niehs.nih.gov/docs/2003/6259/abstract.html?section=children) http://www.cdc.gov/nceh/dls/factsheets/pesticides.htm

[43] http://www.cdc.gov/nceh/clusters/Fallon/Glossary-Non%20Pers.pdf

[44] http://www.nrdc.org/health/pesticides/forgano.asp

[45] Adgate, J.L., Barr, D.B., Clayton, C.A., Eberly, L.E., Freeman, N.C.G., Lioy, P.J., Needham, L.L., Pellizzari, E.D., Quackenboss, J.J., Roy, A., and K. Sexton. 2001. Measurement of children's exposure to pesticides:

(2003) have demonstrated widespread pesticide exposure to the U.S. population, including pregnant women and children, confirming that children are exposed to pesticides prenatally, when they may be particularly vulnerable to adverse health effects.[46]

Risk Factors – Early childhood exposure to organophosphates, carbamates, and pyrethroids can lead to neurobehavioral and neuromuscular problems. There is substantial evidence in animal studies that chronic, low-level exposure to OPs may affect growth and neurologic functioning and neurodevelopment in humans.[47]

Other Research Studies – Eskanazi et al. (1999) cites a longitudinal study of 500 pregnant women and children being at the Center for Children's Environmental Health Research at the University of California, Berkeley that will "*a) characterize OP exposure levels and pathways in pregnant women and their children; b) determine the predictors of OP levels in the body and home; c) describe the exposure-prone behavior of children at different developmental stages using time-activity analysis; and d) follow up the children to 3 years of age to determine whether exposure in utero and/or during the postnatal period is associated with poor neurodevelopment (assessed by tests of the central and autonomic nervous system), slower and stunted growth, and increased prevalence of respiratory symptoms and disease*." Findings from the NCS would supplement those from the Berkeley study and any other similar studies being conducted.

Potential NCS Findings and Subsequent Interventions

NCS hypothesis 2.1, "repeated low-level exposure to nonpersistent pesticides in utero or post-natally increases risk of poor performance on neurobehavioral and cognitive examinations during infancy and later in childhood, especially, for certain agents, among those with genetically decreased paraoxonase activity," examines the link between exposure to nonpersistent pesticides and neurodevelopment. If the NCS is successful at establishing decreased paraoxonase activity (and perhaps other factors) as an effect modifier for the relationship between non-persistent pesticides and neurobehavioral and cognitive development, this could lead to targeted efforts to prevent exposure to sources of nonpersistent pesticides for the population identified with decreased paraoxonase activity.

Considerations in estimating a potential effect of the NCS on cognitive effects of exposure to nonpersistent pesticides include 1) the fact that at least one other significant study is investigating similar effects, 2) the rarity of decreased paraoxonase activity (Battelle 2/20/2004 draft white paper on "Measures for NCS Core Hypotheses" states that "the prevalence of this condition is not known, but is expected to be very small"), and 3) the apparent widespread exposure as found in NHANES and other studies. For cost impact purposes, we will assume that 90 percent of newborns are exposed to nonpersistent pesticides, 1 percent of the population may be affected by this hypothesis's findings, and that half of the subsequent impact will be attributable to the NCS.

Analysis of urinary metabolite levels in a probability-based sample. Environmental Health Perspectives 109(6): 583-590.

[46] Bradman et al, 2003

[47] Eskenazi B, Bradman A, and Castorina R. Exposures of children to organophosphate pesticides and their potential adverse health effects. EHP Supplements Volume 107, Number S3, June 1999.

Regarding the impact on cognitive ability of decreased exposure to nonpersistent pesticides in the targeted at-risk population, as with estimating the effect of reducing mercury exposure we will utilize the research of Grosse et al. on the association between IQ and lifetime earnings. We will also assume, because of a lack of knowledge regarding the specific effects on cognitive ability of in utero and early childhood exposure to nonpersistent pesticides, that the reduction in exposure will lead to an average 1 IQ point gain in the impacted population.

Assumptions Enabling Estimation of NCS Economic Impact

In order to estimate the potential impact of the NCS on pesticide exposure, we make the following assumptions:

- The NCS will study the major types of exposures that are risk factors for nonpersistent pesticide exposure.
- NCS findings can establish links between environmental exposures to pesticides and reduced cognitive ability among children with decreased paraoxonase activity, which can lead to the development of primary prevention measures for this population.
- 90 percent of annual live births are at-risk for nonpersistent pesticide exposure.
- NCS findings will impact 0.5 percent of those at-risk live births each year. We will use a range of 0.3-0.7 for developing cost impact estimates.
- Impact of findings and subsequent prevention efforts will be an average 1 IQ point gain in impacted population.
- The IQ-earnings slope is 1.76, i.e. a 1 IQ point increase leads to a 1.76 percent increase in lifetime earnings. This slope is the conservative estimate from Grosse et al., who used 2.0 as their base case.
- Total estimated lifetime savings (in 2003$) of a 1 IQ point gain in 0.3 to 0.7 percent of at-risk 2003 live births is $245 to 343 million.

10. AUTISM SPECTRUM DISORDERS

Description - Autism spectrum disorders (ASDs) are a group of developmental disabilities that are caused by an abnormality in the brain. People with ASDs tend to have problems with social and communication skills. They also are likely to repeat certain behaviors and to not want change in their daily activities. Many people with ASDs also have unusual ways of learning, paying attention, or reacting to different sensations. ASDs begin during childhood and last throughout a person's life.[48]

Magnitude of the Problem – CDC's ongoing MADDSP study, which tracks the number of children with ASDs and four other disabilities in metropolitan Atlanta, found that in 1996 3.4 of every 1,000 children age 3 through 10 in metropolitan Atlanta had at least one ASD. A 1998 study conducted by CDC investigated the rates of autism among children in Brick Township, New Jersey. The rate of autism among children found in Brick Township was 4.0 per 1,000 children aged 3 through 10, while the prevalence of all ASDs combined was 6.7 cases per 1,000 children. Although the rates in the Brick Township study are higher compared to the MADDSP and other published reports, investigators in other countries are finding rates of autism in the

[48] http://www.cdc.gov/ncbddd/dd/aic/about/default.htm

range of those found in Brick Township. To be conservative, however, we use the lower prevalence estimate from the MADDSP.

Risk Factors - No one knows exactly what causes ASDs, but scientists think that both genetic and environmental factors might play a role.[49] It appears that autism is predominately an inherited condition, however there is no general consensus on what environmental factors are also involved. Some of the suspected environmental causes for which scientific evidence is limited include childhood vaccinations and exposure to chemical toxins.[50]

Other Research Studies – CDC is planning the Children's Longitudinal Development Study (CHILD Study), which will look at what factors make it more likely that a child will have an ASD. CDC is also funding several state projects that will study such factors.

Potential NCS Findings and Subsequent Interventions

NCS Core Hypothesis 2.2 cites "prenatal infection and mediators of inflammation are risk factors for neurodevelopmental disabilities, such as cerebral palsy and autism." Potential findings linking these and other risk factors to autism (or at least one ASD) could lead to medical interventions and prevention measures by physicians during pregnancy to decrease the risk of prenatal infections, as well as to develop guidance to at-risk populations to avoid other environmental triggers that might be identified through the research. Because potential prevention and intervention measures may be incorporated by physicians into treatment of pregnant women, we theorize that they could result in reasonable adoption and successful reduction in cases of autism.

Based on the recommendation of Dr. Marshalyn Yeargin-Allsopp of CDC, we made the assumption that six percent of autism cases are potentially modifiable. We then made the further assumption that the prevention measures adopted in response to findings related to prenatal infection and mediators of inflammation may lead to a 1/6 reduction in autism among those six percent – a total reduction of 1 percent. Dr. Yeargin-Allsopp's recommendation is based on the findings in Fombonne (1999) that cites that "medical conditions of potential causal significance were found in 6% of subjects with autism."[51] Although it is not clear whether the other 94 percent of cases might be associated with prenatal infection or mediators of inflammation, we utilize the six percent estimate to develop the estimated cost impact.

Assumptions Enabling Estimation of NCS Economic Impact

In order to estimate the potential impact of the NCS on autism, we make the following assumptions:

- The NCS will study the major types of exposures that are risk factors for autism.
- NCS findings related to the association between prenatal infection and mediators of inflammation and autism can lead to the development of primary prevention measures that can reduce certain incidence of autism.
- 0.34 percent of the 2003 birth cohort (13,600 children) will develop at least one ASD between the ages of 3 and 10.

[49] http://www.cdc.gov/ncbddd/dd/aic/about/default.htm
[50] http://www.autism.org/adviceforparents.html
[51] Fombonne, E. The epidemiology of autism: a review. Psychol Med 29:769-786, 1999.

- Six percent of all autism cases can potentially be impacted by findings related to prenatal infection and mediators of inflammation and other environmental risk factors.
- Autism can be prevented in one-sixth of the in-scope autism cases (or 1 percent of all cases) via measures based on NCS findings. We use a range of 0.5 to 1.5 percent of all cases for purposes of the estimating cost impact.
- Total estimated 2003 cost of autism is $40.6 billion (based on UK autism cost research).

These assumptions would enable estimated economic savings in the range of $0.2-0.6 billion each year.