

## **Targeted Research Area: Asthma and Respiratory Illnesses**

### **General Information on Asthma and Respiratory Illnesses**

- **Prevalence and incidence of asthma:**
  - The reported prevalence of asthma has increased dramatically in children and adults over the past decade. An estimated 4.8 million children in the United States (1 in 15) under the age of 18 have asthma.<sup>1</sup>
  - The epidemic of asthma and allergic disorders is occurring in western societies/First World countries.<sup>2</sup>
  - Asthma rates have increased by 160% in the past 15 years in children under the age of 5.<sup>3</sup>
  
- **Mortality from asthma:**
  - The death rate from asthma for children ages 19 and younger increased by 78% between the years 1980 and 1993.<sup>4</sup>
  - Nearly 300 children die each year from asthma.<sup>5</sup>
  
- **Disease severity/disease burden**
  - Each year 150,000 children are hospitalized for asthma.<sup>6</sup>
  - Asthma is a leading cause of school absenteeism, resulting in 10 million missed school days per year. It often causes interrupted sleep, limited activity, and disruptions of family and caregiver routines.<sup>7</sup>
  - Severity of the disease has increased as seen in increased hospitalization rates. One study found that the odds of an adverse outcome (i.e., intubation, cardiopulmonary arrest, or death) among children hospitalized for asthma in California doubled between 1986 and 1993.<sup>8</sup>
  - Two surveys found that many inner city children took no medication for their asthma, despite frequent symptoms, ER visits, and absences from school. Inner city children who are on medications for asthma rely heavily on beta adrenergic agonists alone, which could lead to more unstable asthma. In one study of inner city children with asthma, 18% of the children were reported to have low birth

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<sup>1</sup> Environmental Protection Agency. *Asthma and Upper Respiratory Illnesses*. Available at <http://www.epa.gov/children/asthma.htm>

<sup>2</sup> Abramson MJ, Walters EH. The epidemic of asthma: too much allergen or not enough infection? *Medical Journal of Australia* 2000;172(3):119-21.

<sup>3</sup> Environmental Protection Agency. *Asthma and Upper Respiratory Illnesses*. Available at <http://www.epa.gov/children/asthma.htm>

<sup>4</sup> Centers for Disease Control and Prevention, National Center for Environmental Health. *Asthma's Impact on Children And Adolescents*. Available at <http://www.cdc.gov/nceh/airpollution/asthma/children.htm>

<sup>5</sup> Environmental Protection Agency. *Asthma and Upper Respiratory Illnesses*. Available at <http://www.epa.gov/children/asthma.htm>

<sup>6</sup> Ibid.

<sup>7</sup> President's Task Force on Environmental Health Risks and Safety Risks to Children. *Asthma and the Environment: A Strategy to Protect Children*. Available at <http://epa.gov/children/whatwe/fin.pdf>

<sup>8</sup> Pandya R, Solomon G, Kinner A, Balmes JR. Diesel exhaust and asthma: hypotheses and molecular mechanisms of action. *Environmental Health Perspectives* 2002;110 (Suppl 1):103-12.

weight, 25% were in an intensive care unit at birth, and 10% were on a respirator.<sup>9</sup>

- **Cost to individual/family/society/healthcare system:**
  - In the U.S., the estimated annual cost of treating asthma in children under the age of 18 is \$3.2 billion.<sup>10</sup>
  
- **Special populations**
  - Asthma-related hospitalizations for inner-city and minority children have risen disproportionately.<sup>11</sup>
  - Minority populations also suffer a disproportionately higher rate of death from asthma. In 1995, the death rate for asthma in African-American children was four times the death rate in Caucasian children.<sup>12</sup>
  - There are racial differences in prevalence even when adjusting for socioeconomic factors. According to NHANES II data, the rate of asthma in children 6 months to 11 years of age was 3% in Caucasians and 7.2% in African-Americans. The greatest increase in prevalence has been reported among inner-city children and young adults living in the U.S. African-American children have higher prevalence, even when adjusting for socioeconomic factors.<sup>13</sup>

*Hypotheses 1 – 5, described on the following pages, are associated with the Asthma and Respiratory Illnesses targeted research area.*

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<sup>9</sup> Eggleston PA, Buckley TJ, Breyse PN, Wills-Karp M, Kleeberger SR, Jaakkola JJ. The environment and asthma in U.S. inner cities. *Environmental Health Perspectives* 1999;107(Suppl 3):439-50.

<sup>10</sup> American Lung Association. *Asthma in Children Fact Sheet (March 2002)*. Available at: <http://www.lungusa.org/asthma/ascpedfac99.html>

<sup>11</sup> Environmental Protection Agency. *Asthma and Upper Respiratory Illnesses*. Available at <http://www.epa.gov/children/asthma.htm>

<sup>12</sup> President's Task Force on Environmental Health Risks and Safety Risks to Children. *Asthma and the Environment: A Strategy to Protect Children*. Available at <http://epa.gov/children/whatwe/fin.pdf>

<sup>13</sup> Eggleston PA, Buckley TJ, Breyse PN, Wills-Karp M, Kleeberger SR, Jaakkola JJ. The environment and asthma in U.S. inner cities. *Environmental Health Perspectives* 1999;107( Suppl 3):439-50.

**Hypothesis #1: Infections in early childhood have a protective effect against asthma.**

***General Information Related to Hypothesis #1***

- **Frequency/load of exposure to daycare-related infections:** In 1995, approximately 60% of children in the U.S. were attending day care. Day care attendance is associated with an increased risk of infections.<sup>14</sup>
- **Frequency/Load of exposure to infections:** Children in First World countries now suffer fewer infections as a result of improved hygiene, smaller families, and effective early-childhood vaccination programs. Another factor that has led to reduced exposure to infections has been the use of antibiotics in early childhood.<sup>15</sup>
- **Findings from recent research (targeted search):** Information reported in the following four studies contributed to the above-mentioned hypothesis.

Study #1: Celedon JC, Litonjua AA, Ryan L, Weiss S, Gold DR. Day care attendance, respiratory tract illnesses, wheezing, asthma, and total serum IgE level in early childhood. Archives of Pediatrics & Adolescent Medicine 2002;156(3):241-5.

Study #1 hypothesis being tested: Day care-related infections in the first year of life are protective against wheezing and asthma in the first four years of life among children with a parental history of atopy.

Study #1 findings: The study found that day care attendance in early life was protective against the development of atopy by 2 years of age. However, there was no significant association between day care attendance in the first year of life and recurrent wheezing or asthma at 4 years of age. A protective effect of day care attendance in early life against wheezing may not be observed until after 4 years of age. The authors state that the lack of an inverse association between day care attendance and asthma or wheezing in early childhood is likely because wheezing in early childhood may be related to infections in children with small airways or to allergic inflammation of the airways. Because of the increased risk of respiratory infections associated with day care attendance in the first year of life (but inverse association with atopy), it may be impossible to observe a protective effect of day care attendance on wheezing until the children are older. The authors call for further follow-up study on their cohort to help clarify the relation between day care attendance and or respiratory tract illnesses in early life and childhood asthma and atopy.

<sup>14</sup> Celedon JC, Litonjua AA, Ryan L, Weiss S, Gold DR. Day care attendance, respiratory tract illnesses, wheezing, asthma, and total serum IgE level in early childhood. Archives of Pediatrics & Adolescent Medicine 2002;156(3):241-5.

<sup>15</sup> Droste JH, Wieringa MH, Weyler JJ, Nelen VJ, Vermeire PA, Van Bevers HP. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? Clinical and Experimental Allergy 2000;30:1547-53.

Study #2: Illi S, vonMutius E, Lau S, Bergmann R, Niggemann B, Sommerfeld C, Wahn U. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001;322:390-5.

Study #2 hypothesis being tested: Infections in early childhood have a protective affect against asthma.

Study #2 findings: The study found that the total burden of infection as well as certain viral infections, namely repeated episodes of runny nose and viral infections of the herpes type, before age 3 were shown to have an inverse relation with the development of asthma by age 7. However, the study also found that repeated lower respiratory tract infections early in life were positively associated with the subsequent development of asthma. The authors suggest that viral infections other than lower respiratory tract infections early in life may stimulate the immature immune system towards the Th1 phenotype, reducing the risk for developing asthma up to school age. The authors further suggest there is a window of vulnerability, with the immature immune system being most susceptible to the influence of infections with the first year of life.

Study #3: Abramson MJ, Walters EH. The epidemic of asthma: too much allergen or not enough infection? *Medical Journal of Australia* 2000;172(3):119-21.

Study #3 hypothesis being tested: The absence of infection in childhood might increase the risk of atopy. Childhood infections seem to be important in normal maturation of the immune system (Th1 immunity), with asthma as a manifestation of a persistent "immature" immune system.

Study #3 findings: Studies of cohorts that have survived infections such as measles and tuberculosis, have shown a reduced risk of atopy and asthma. However, the role of vaccinations in relation to infections is still not clear. The authors suggest that the relative absence of immunologically modifying childhood infections or environmental adjuvants is likely to be a factor in the epidemic of asthma and allergic disorders in Western societies. Further, the authors identify a need for research on the role of vaccinations, and research to confirm effects of antibiotic use and determine associated immunological mechanisms responsible.

Study #4: Droste JH, Wieringa MH, Weyler JJ, Nelen VJ, Vermeire PA, Van Bevers HP. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clinical and Experimental Allergy* 2000;30:1547-53.

Study #4 hypothesis being tested: The use of antibiotics in the first year of life may lead to subsequent development of asthma and allergic disorders.

Study #4 findings: The prevalence of asthma, hay fever, and eczema were significantly higher in children who used antibiotics in the first year of life and who had a parent with hay fever. For children without parental hay fever, there were no significant associations between antibiotic use and asthma or allergy. The study supported the hypothesis that the use of antibiotics in the first year of life was shown to be significantly

associated with the development of asthma only in children who are predisposed to atopic immune responses. The authors suggest that prospective studies should be conducted in populations with different "risk levels" of asthma and allergic disorders to better understand the association between early childhood infections and development of asthma and the role of genetic factors in this process.

**Hypothesis #2: Endotoxin exposure in childhood may have a protective effect against the development of asthma.**

***General Information Related to Hypothesis #2***

- **Findings from recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Liu AH. Endotoxin exposure in allergy and asthma: Reconciling a paradox. *Journal of Clinical Immunology* 2002;109(3):379-92.

Study #1 hypothesis being tested: Endotoxins may have a positive as well as a negative effect on development of asthma.

Study #1 findings: Some studies indicate that endotoxins have a protective effect against the development of asthma, supporting the hypothesis that microbial exposures promote the Th1-type immune development. Endotoxin exposure in farming communities, for example, has been associated with a reduced risk of asthma. However, there are also studies pointing to the negative influence of endotoxin exposure. Some studies have shown that endotoxins can induce varying degrees of airflow obstruction and neutrophil inflammation in non-asthmatic subjects. The author suggests that studies of endotoxin exposure and asthma hint that the benefits of exposure depend on the importance of timing, dosage, environmental cofactors, and genetics. The author calls for more research, particularly for prospective studies in different locales, to better determine the role of endotoxin exposure.

Study #2: Douwes J, Pearce N, Heederik D. Does environmental endotoxin exposure prevent asthma? *Thorax* 2002;57(1):86-90.

Study #2 hypothesis being tested: Respiratory exposure to endotoxins may confer a protective effect against development of atopy and asthma.

Study #2 findings: A few studies have demonstrated a protective effect of endotoxins against atopy through promotion of the Th1 pathway of the immune system during fetal and perinatal development. However, other studies show that endotoxin exposure can exacerbate pre-existing asthma and may be a causal factor in development of non-allergic asthma. The authors suggest that caution should be taken regarding the hypothesis. A protective effect has only been established for atopy. Exposure to endotoxins may prevent primary causation of allergic asthma, but it may be both a primary and secondary cause of non-allergic asthma. The study's findings suggest that the discrepancy in the role of endotoxins may be related to the timing (prenatal and neonatal vs. child and adult life) and dose of exposure. The authors call for further research on these aspects of endotoxin exposure.

Study #3: Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Farm environment in childhood prevents the development of allergies. *Clinical and Experimental Allergy* 2000 Feb;30(2):201-8.

Study #3 hypothesis being tested: A farm environment has a protective effect on asthma, wheezing, and atopic disorders.

Study #3 findings: The study found that childhood farm environments reduced the risk for physician-diagnosed asthma and episodic wheezing analyzed together. The study suggests that childhood farm environments have a protective effect against allergic rhinitis and/or conjunctivitis, and more weakly against asthma and wheezing, irrespective of family size. Environmental exposure to immune modulating agents, such as environmental mycobacteria and actinomycetes, favoring manifestation of a non-atopic phenotype (Th1) could explain this finding. The authors suggest that more research is needed to study interactions between exposure to microbes and asthma.

**Hypothesis #3:** Maternal exposures to environmental agents (e.g., indoor allergens or environmental tobacco smoke), behaviors (e.g., diet, history of asthma) or complications (e.g., early labor, maternal health complications) during pregnancy may contribute to the development of asthma and other respiratory illnesses in offspring.

***General Information Related to Hypothesis #3***

- **Frequency/load of exposure to environmental tobacco smoke (ETS) and the effect of maternal diet:** ETS exposure has decreased significantly in the past two decades, even amongst smoking parents. Asthma development may be the result of an increasing decline in host resistance due to reduced consumption of fruit and vegetables and resulting vitamin deficiencies.
- **Findings from recent research (targeted search):** Information reported in the following six studies contributed to the above-mentioned hypothesis.

Study #1: Annesi-Maesano I, Moreau D, Strachan D. In utero perinatal complications preceding asthma. *Allergy* 2001;56:491-97.

Study #1 hypothesis being tested: Various in utero and perinatal influences contribute to the development and severity of asthma in childhood.

Study #1 findings: Controlling for confounders that predispose one to health complications in pregnancy or child asthma (including premature birth and its associated complications), the study found that maternal health complications during pregnancy, labor, or delivery, as well as neonatal illness in the first week of life were associated with a risk of a child developing asthma. In particular, the risk increased with early and threatened labor and malpresentation and malposition of the fetus. The results provide further evidence that in utero and perinatal complications may increase the risk of developing asthma. Unidentified processes that lead to some of these complications may be associated with fetal "programming," whereby a stimulus or insult at a critical period of development leads to permanent effects on the body's structure, physiology, and metabolism. The authors suggest that more detailed studies of specific perinatal complications are needed, as well as studies of how genetic and early life factors interact with the developing lung and lead to the onset of asthma.

Study #2: Nafstad P, Magnus P, Jaakkola JJK. Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications. *Journal of Allergy and Clinical Immunology* 2000;106(5):867-73.

Study #2 hypothesis being tested: Events occurring during fetal life may affect the development of the immune and respiratory systems and increase the risk of asthma and allergic diseases. The study further hypothesized that complications related to the pathophysiology of the uterus (e.g., antepartum hemorrhage, preterm contractions,

insufficient placenta) would influence the fetus differently than maternally related complications (i.e., complications representing systemic diseases).

Study #2 findings: The study found that children (followed up to age 4) with uterus-related complications had a higher risk of bronchial obstruction, asthma, and allergic rhinitis compared with children without such complications. The study found that the risk of bronchial obstruction during the first two years of life and that of asthma at the age of 4 years were associated with uterus-related complication in pregnancy but not with maternally related pregnancy complications or cesarean delivery. Increasing maternal age at delivery was negatively associated with the risk of asthma and allergic rhinitis at age 4.

Study #3: Denson KWE. Passive smoking in infants, children and adolescents. The effects of diet and socioeconomic factors. *International Archives of Occupational and Environmental Health* 2001;74(8):525-532.

Study #3 hypothesis being tested: The diet of a mother during pregnancy or breast feeding may have greater contributory effect than ETS on the development of asthma.

Study #3 findings: Studies of ETS exposure and asthma have made little allowance for confounding by the diet of the mother and the diet of children in smoking households. Studies have linked vitamin C, vitamin E, and beta carotene deficiency to asthma. Consumption of fruit and vegetables were found to have beneficial effects on lung function. The authors suggest that smoking is often inextricably linked to other socioeconomic factors, such as diet, which may be causal factors for asthma and respiratory diseases.

Study #4: London SJ, Gauderman WJ, Avol E, Rappaport EB, Peters JM. Family history and risk of early-onset persistent, early-onset transient, and late onset asthma. *Epidemiology* 2001;12(5):577-83.

Study #4 hypothesis being tested: Genetic susceptibility, approximated by parental history of asthma and allergy, modulates the association between very early life exposures such as maternal smoking and the various asthma subtypes (i.e., early-onset persistent, early-onset transient, and late onset asthma).

Study #4 findings: The study found a stronger association between parental history of asthma and early-onset persistent asthma. They also found that sibling history of asthma (when in the absence of parental history) was associated with early-onset persistent asthma more than with the other subtypes. Numerous studies have shown a strong relationship between asthma risk and family history of asthma, but few have related family history to the asthma subtypes, each of which has different associations with various risk factors. The authors note that few other studies have looked at the influence of family history of asthma on the different subtypes of asthma, which differ in their associations with various risk factors.

Study #5: Peden DB. Development of atopy and asthma: candidate environmental influences and important periods of exposure. *Environmental Health Perspectives* 2000;108 Suppl 3:475-82.

Study #5 hypothesis being tested: Environmental agents modulate immune processes in the development of atopy and asthma.

Study #5 findings: Maternal exposure to food allergens has been linked to fetal levels of IgE and atopic development in infants. Prenatal and postnatal exposures to other allergens can affect immune processes and lead to atopic phenotype. Some studies have shown that seasonal airborne allergens prevalent in first month of life seem to predict eventual atopic disease related to that allergen later in childhood. Development of atopy is a complex immune process. In addition to any genetic predisposition that may exist, environmental agents can modulate this process and lead to expression of an atopic phenotype and development of asthma. Prenatal maternal exposures and postnatal exposures in the first year of life may have the greatest influence on the asthma development.

Study #6 Perera FP, Illman SM, Kinney PL, Whyatt RM, Kelvin EA, Shepard P, et al. The challenge of preventing environmentally related disease in young children: community-based research in New York City. *Environmental Health Perspectives* 2002;110(2):197-204. *(Note: This study is also cited under the research areas of childhood cancer, environmental toxicants, and neurodevelopmental disorders.)*

Study #6 hypothesis being tested: Prenatal and postnatal exposure to damage, and increased risk of cancer.

Study #6 findings: Environmental toxicants can modify the formation and maturation of the lungs. In utero sensitization to specific allergens can occur independently of maternal sensitization, putting child at higher risk for asthma. Neurochemical and behavioral effects arise from exposure to toxicants during critical windows of fetal development. Fetuses also clear toxicants less efficiently than adults and are more vulnerable to genetic damage, increasing subsequent cancer risk. Nutritional deficits in maternal diet have been linked to development of asthma in the child. Gene-environment interactions and psychosocial factors can also make a fetus or newborn more susceptible to disease. Some studies suggest that women who live in violent, crime-ridden neighborhoods experience pregnancy complications and adverse birth outcomes. Prenatal and postnatal exposure to environmental toxicants can lead to respiratory disease, impaired neurological development, genetic damage, and increased risk of cancer. Nutrition, gene-environment interaction, and psychosocial stressors are cofactors that compound the susceptibility of the fetus and newborn.

**Hypothesis #4:** Exposures to environmental agents found in the home, such as environmental tobacco smoke (ETS) or indoor allergens, in early childhood may lead to the development or exacerbation of asthma.

***General Information Related to Hypothesis #4***

- **Frequency/load of exposure to allergens:** More than 80% of asthmatic children in the U.S. are allergic, suggesting that if asthmatics are specifically sensitized to a particular allergen, exposure to high levels of that allergen may exacerbate their asthmatic symptoms.<sup>16</sup>
- **Frequency/load of exposure to secondhand smoke and ETS:** 29% of all homes in the U.S. permit exposure of children to secondhand smoke and 88% of all children have some level of documented exposure to ETS.<sup>17</sup>
- **Frequency/Load Exposure to residential risk factors:** Residential exposures (including pets, ETS, use of gas stove or oven) account for 44.4% of physician-diagnosed asthma in children 6-16 years old.<sup>18</sup>
- **Costs to individual/family/society/healthcare system:** There is an estimated total cost of \$405 million annually (in 1997 dollars) for children and adolescents aged 6-16 who have asthma attributable to residential risk factors. Including costs for children < 6 years old, total cost increases to \$807 million annually.<sup>19</sup>
- **Findings from recent research (targeted search):** Information reported in the following two studies contributed to the above-mentioned hypothesis.

Study #1: Lanphear BP, Kahn RS, Berger O, Auinger P, Bortnick SM, Nahhas RW. Contribution of residential exposures to asthma in U.S. children and adolescents. *Pediatrics* 2001;107(6):E98.

Study #1 hypothesis being tested: Residential risk factors contribute to the development of asthma.

Study #1 findings: The study found that having a pet or an allergy to a pet were the predominant risk factors for asthma. Hypersensitivity to dust mite and cockroach allergens was also a major risk factor. In addition, exposure to ETS in early childhood was found to be a risk factor for asthma. The authors found that residential risk factors accounted for 44% of physician-diagnosed asthma in children studied. An estimated 5% of children with a residential risk factor were hospitalized in the past 12 months; 40%

<sup>16</sup> Gold DR. Environmental tobacco smoke, indoor allergens, and childhood asthma. *Environmental Health Perspectives* 2000;108 Suppl 4:643-51.

<sup>17</sup> President's Task Force on Environmental Health Risks and Safety Risks to Children. *Asthma and the Environment: A Strategy to Protect Children*. Available at <http://epa.gov/children/whatwe/fin.pdf>

<sup>18</sup> Lanphear BP, Kahn RS, Berger O, Auinger P, Bortnick SM, Nahhas RW. Contribution of residential exposures to asthma in U.S. children and adolescents. *Pediatrics* 2001;107(6):E98.

<sup>19</sup> Ibid.

had at least one emergency department visit or clinic visit for wheezing in the past 12 months.<sup>20</sup>

Study #2: Gold DR. Environmental tobacco smoke, indoor allergens, and childhood asthma. *Environmental Health Perspectives* 2000;108(Suppl 4):643-51.

Study #2 hypothesis being tested: Environmental tobacco smoke (prenatal and postnatal exposure) and indoor allergens influence the development and exacerbation of asthma.

Study #2 findings: Prenatal (maternal smoking during pregnancy) ETS exposure can alter airway architecture and/or bronchial hyper-reactivity. Both prenatal and postnatal ETS exposure increase risk of lower respiratory illnesses and may potentiate the immune response to allergen inhalation. Studies suggest that in already allergic populations, indoor allergen exposure may increase the risk of sensitization to a specific allergen and increase risk of developing asthma. The authors suggest that ETS and indoor allergens are potential factors that influence the development of asthma through influencing the development of allergy, the expression of allergy in the lung, or the expression of bronchial reactivity. The authors note that further research is needed to evaluate the influence of the following environmental factors on development of asthma: early life infections, antibiotic use, vaccination practices, exposure to endotoxin, exposure to chronic parasitism, factors influencing gut flora, diet, obesity, a sedentary indoor lifestyle, and stress.

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<sup>20</sup> Ibid.

**Hypothesis #5: Exposure to air pollutants such as ozone and particulate matter may lead to the development or exacerbation of asthma.**

***General Information Related to Hypothesis #5***

- **Frequency/load of exposure to ozone:** 25% of children in the U.S. live in areas in which EPA limits for ozone are regularly exceeded.<sup>21</sup>
- **Frequency/load of exposure to diesel exhaust particles (DEPs):** Buses, trucks, and other heavy industrial transport vehicles are major sources of ambient diesel exhaust pollution. Use of diesel fuel has increased in the U.S.: the number of miles traveled by commercial trucks has increased by 235% between 1950 and 1985. In 1996, diesel exhaust comprised a quarter of the nitric oxide (NO) smog precursors released nationally in the U.S.<sup>22</sup>
- **Special populations:** Children living along trucking routes or in areas of heavy trucking traffic are at a particular risk for chronic exposure to DEPs and development of asthmatic symptoms.<sup>23</sup>
- Exposure to ETS, NO<sub>2</sub>, O<sub>3</sub>, and particulate matter is higher in inner city homes. NO<sub>2</sub> levels are frequently in excess of U.S. EPA standards.<sup>24</sup>
- **Findings from recent research (targeted search):** Information reported in the following four studies contributed to the above-mentioned hypothesis.

Study #1: McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, et al. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002;359(9304):386-91.

Study #1 hypothesis being tested: Children engaged in team sports in polluted communities might also be at high risk for developing asthma.

Study #1 findings: The study found that in communities with high ozone concentrations, there is an increased risk of developing asthma in children playing three or more sports compared to children playing no sports. Time spent outside was associated with a higher incidence of asthma in areas of high ozone. In areas of low ozone, sports and time spent outside had no effect. The authors suggest that exposure to ozone may modify the effects of sports on the development of asthma in some children. This exposure is dependent on air pollutant concentrations in the community and children's time spent and physical activity exerted while outside.

<sup>21</sup> President's Task Force on Environmental Health Risks and Safety Risks to Children. *Asthma and the Environment: A Strategy to Protect Children*. Available at <http://epa.gov/children/whatwe/fin.pdf>

<sup>22</sup> Pandya R, Solomon G, Kinner A, Balmes JR. Diesel exhaust and asthma: hypotheses and molecular mechanisms of action. *Environmental Health Perspectives* 2002;110 Suppl 1:103-12.

<sup>23</sup> Ibid.

<sup>24</sup> Eggleston PA, Buckley TJ, Breyse PN, Wills-Karp M, Kleeberger SR, Jaakkola JJ. The environment and asthma in U.S. inner cities. *Environmental Health Perspectives* 1999;107(Suppl 3):439-50.

Study #2: Pandya R, Solomon G, Kinner A, Balmes JR. Diesel exhaust and asthma: hypotheses and molecular mechanisms of action. *Environmental Health Perspectives* 2002;110(Suppl 1):103-12.

Study #2 hypothesis being tested: Particulate matter in diesel exhaust may play a role in causing asthma.

Study #2 findings: One study found that children living near busy diesel trucking routes have decreased lung function. A study of Italian children living on streets with heavy trucking traffic were 60-90% more likely to report asthmatic symptoms. Studies such as these indicate that exposure to DEPs are associated with inflammatory and immune responses involved in asthma, however, questions remain regarding the underlying mechanisms. The authors suggest observational studies of children be performed, including quantitative assessments of DEP exposure and airway function. They also note that research is needed to investigate the clinical relevance of the observed adjuvant effect of co-exposure to DEPs and allergens.

Study #3: Goldsmith CA, Kobzik L. Particulate air pollution and asthma: a review of epidemiological and biological studies. *Reviews on Environmental Health* 1999;14(3):121-34.

Study #3 hypothesis being tested: Air pollution causes exacerbation of asthma and increases asthma morbidity.

Study #3 findings: Epidemiological studies have shown a marked correlation of asthma morbidity to air pollution particle concentration. Biological studies conducted indicate that particles can increase asthmatic symptoms. Particles can affect the pulmonary environment by creating an allergic profile of cytokines and immunoglobulins, and by directly affecting lung cells. There is a substantial body of evidence indicating that air pollutants adversely affect asthmatic individuals. The authors state that more research is needed, including real-world experiments to confirm the findings of biological studies and the effects of particle exposure in conjunction with co-pollutants such as ozone.

Study #4: Eggleston PA, Buckley TJ, Breysse PN, Wills-Karp M, Kleeberger SR, Jaakkola JJ. The environment and asthma in U.S. inner cities. *Environmental Health Perspectives* 1999;107(Suppl 3):439-50.

Study #4 hypothesis being tested: Genetic predisposition to form IgE to allergenic proteins on airborne particles is further affected by increased exposure to allergens and air pollutants and the psychosocial stresses of living in poor inner city neighborhoods.

Study #4 findings: ETS, NO<sub>2</sub>, O<sub>3</sub>, and particulate matter have all been shown to be in excess in inner city homes and neighborhoods and have been associated with the development and/or exacerbation of asthma. The authors suggest that genetic predisposition to allergic sensitization can lead to asthma. In addition, factors found in urban environments such as increased indoor allergens, and underlying psychosocial factors can further affect susceptibility to asthma.

## **Targeted Research Area: Childhood Cancers**

### **General Information on Childhood Cancers**

- **Prevalence and incidence of childhood cancers:**
  - Approximately 8,600 U.S. children between the ages 0 and 14 will be diagnosed with cancer in 2002, according to the American Cancer Society and SEER Cancer Statistics Review. Overall, childhood cancer rates have increased nearly 21% from 1975 to 1998 and appear to be increasing at approximately 1% every year.<sup>25</sup>
  - About one third of childhood cancers are leukemias; approximately 2,700 children (<age 15) were diagnosed with leukemia in 2001.<sup>26</sup> Acute lymphocytic leukemia (ALL) and brain tumors have increased particularly in children 0 to 5 years old.<sup>27</sup>
  - Childhood cancer rates have increased nearly 21% from 1975 to 1998 and are increasing at a steady rate of approximately 1% per year.<sup>28</sup>
  - Nearly 12,000 children under the age of 19 are diagnosed with cancer each year in the U.S. The most frequently diagnosed childhood cancers include leukemias, CNS tumors, neuroblastoma, Hodgkin's disease, non-Hodgkin's lymphoma, Wilms' tumor, retinoblastoma, soft tissue sarcomas, and germ cell tumors. The incidence of ALL has been increasing at about 1% per year; incidence of CNS tumors has increased at about 1.5% per year.<sup>29</sup>
- **Mortality from childhood cancers:**
  - Cancer is the leading cause of death from disease in children under 15 and the second leading cause of death in most age groups.<sup>30</sup>
  - The most common tumors in infancy and childhood are neuroblastoma, leukemia, and renal tumors, resulting in about 10,000 cancer deaths per year in the U.S.
- **Disease severity/disease burden:** This information was not readily available to The Lewin Group.
- **Cost to individual/family/society/healthcare system:** This information was not readily available to The Lewin Group.

<sup>25</sup> Massey-Stokes M, Lanning B. Childhood cancer and environmental toxins: The debate continues. *Family & Community Health* 2002;24(4):27-38.

<sup>26</sup> National Cancer Institute, National Institutes of Health. Cancer Facts: National Cancer Institute Research on Childhood Cancers. Available at: [http://cis.nci.nih.gov/fact/6\\_40.htm](http://cis.nci.nih.gov/fact/6_40.htm)

<sup>27</sup> Massey-Stokes M, Lanning B. Childhood cancer and environmental toxins: The debate continues. *Family & Community Health* 2002;24(4):27-38.

<sup>28</sup> Bowman P, Oblender M, Oeffinger KC, Ward J. Childhood cancer and environmental toxins: the debate continues. *Family & Community Health* 2002;24(4):27-38.

<sup>29</sup> Ross JA, Swensen AR. Prenatal epidemiology of pediatric tumors. *Current Oncology Reports* 2000;2(3):234-41.

<sup>30</sup> Bowman P, Oblender M, Oeffinger KC, Ward J. Childhood cancer and environmental toxins: the debate continues. *Family & Community Health* 2002;24(4):27-38.

- **Frequency/load of exposure:** The frequency/load of exposure varies depending on the type of exposure and associated disease outcome.
- **Special populations:** Special populations in which either the exposure or disease outcome or both are more prevalent vary.

*Hypotheses 6 – 10, described on the following pages, are associated with the Childhood Cancers targeted research area.*

**Hypothesis #6:** Exposure to electromagnetic fields (EMFs) may increase the risk of childhood cancers such as leukemia (acute lymphocytic and T-cell) and brain tumors.

***General Information Related to Hypothesis #6***

- **Frequency/load of exposure to EMFs:** Residential and industrial use of electricity for power, heating, and lighting has increased exposure to EMF in the past few decades.
- **Special populations:** Jobs that place workers near high-voltage substations and electricity should receive attention regarding occupational exposure related diseases.
- **Findings from recent research (targeted search):** Information reported in the following five studies study contributed to the above-mentioned hypothesis.

Study #1: Ahlbom IC, Cardis E, Green A, Linet M, Savitz D, Swerdlow A. Review of the epidemiologic literature on EMF and Health. Environmental Health Perspectives 2001;109(Suppl 6):911-33.

Study #1 hypothesis being tested: EMF exposure is a possible risk factor for chronic diseases, including childhood cancer such as leukemia, and may also affect other endpoints including pregnancy outcomes.

Study #1 findings: Some studies have indicated an association between postnatal exposures above 0.4  $\mu\text{T}$  and childhood leukemia. The mechanism by which exposure could lead to cancer, however, is unknown. Current evidence does not support hypothesis that maternal exposure to residential or occupational EMF is associated with adverse pregnancy outcomes. There is no chronic disease outcome for which an etiological relation to EMF exposure can be regarded as established. Childhood leukemia in relation to postnatal exposure has been most evident of an association.

Study #2: Schuz J, Grigat JP, Brinkmann K, Michaelis J. Residential magnetic fields as a risk factor for childhood acute leukemia: results from a German population-based case-control study. International Journal of Cancer 2001;91(5):728-35.

Study #2 hypothesis being tested: Exposure to residential power-frequency (50 Hz) magnetic fields above 0.2  $\mu\text{T}$  increases risk of childhood leukemia. Risk is increased with exposure to stronger magnetic fields during the night.

Study #2 findings: The study found evidence of a weak association between exposure to residential magnetic fields, in general, and leukemia. There was, however, a significant association between childhood leukemia and magnetic field exposure at night. The authors suggest that although there is evidence of an association between leukemia and exposure to magnetic fields, this association neither proof nor a breakthrough. Evidence of an association with magnetic field exposure at night may warrant further study. Increased leukemia risk from night exposure to magnetic fields may be due to suppression of nocturnal production and release of melatonin which is assumed to have

oncostatic capabilities. Another hypothesis that might account for any association is that children with prenatal genetic abnormalities require a postnatal event such as exposure to magnetic fields for full development of leukemia.

Study #3: Bowman P, Oblender M, Oeffinger KC, Ward J. Childhood cancer and environmental toxins: the debate continues. *Family & Community Health* 2002;24(4):27-38.

Study #3 hypothesis being tested: Exposure to environmental toxins and other risk factors (e.g., EMFs, radon, pesticides, solvents, parental occupational exposure, diet, ETS, alcohol, and infection during preconception, in utero, and postnatal periods) can lead to an increased risk of childhood cancers, particularly acute lymphocytic leukemia (ALL) and brain tumors.

Study #3 findings: The links between many environmental agents, including EMFs, radon, pesticides, solvents, parental occupational exposure, diet, ETS, alcohol, and infection, and cancers such as leukemia remain speculative. The authors suggest that childhood cancers are most likely a result of an interaction between genetic predisposition, environmental factors, and susceptibility. The authors call for further studies focused on genetic predisposition.

Study #4: Bolande RP. Prenatal exposures and childhood cancer. *Pediatric and Developmental Pathology* 1999;2(3):208-14.

Study #4 hypothesis being tested: Some childhood cancers are initiated in the embryo, fetus, or parental germ cells as a result of prenatal or preconceptional exposures to electromagnetic fields, paint, hydrocarbon, cigarette smoke, etc.

Study #4 findings: The study discusses findings from research on environmental toxicants as causal factors for childhood cancers. DES, for example has been identified as a transplacental carcinogen. HTLV, an oncogenic retrovirus, has been shown to be transmittable from mother to child through breast milk and can lead to T-cell leukemia. The authors found that no specific parental occupation or exposure or etiologic agent has been firmly established that could preconceptionally initiate or cause a childhood cancer. Prenatal carcinogenicity of irradiation remains unclear and controversial; studies have varied in success in showing an association of childhood tumors and prenatal exposure to ionizing irradiation. Heritable factors are important in less than 10% of childhood tumors. Most are the result of environmental carcinogenic agents which have yet to be identified. The authors suggest that genetic susceptibility, host resistance, and the embryonic environment may also play a role in childhood cancers.

Study #5: Ross JA, Swensen AR. Prenatal epidemiology of pediatric tumors. *Current Oncology Reports* 2000 May;2(3):234-41.

*(Note: This study is cited under childhood cancers and other exposures – infectious agents and paternal/maternal smoking.)*

Study #5 hypothesis being tested: Infectious agents such as mycoplasma pneumonia and hepatitis A may lead to leukemia. There may be a dose-response relationship in the

association between in utero exposure to radiation and childhood leukemia. Paternal smoking has a more powerful effect on childhood cancer than maternal smoking. EMF exposure may be associated with leukemia.

Study #5 findings: One study in Greece indicated that infants exposed in utero to radiation had a higher incidence of leukemia and that there was a positive dose-response relationship between incidence and radioactivity in the region. Most epidemiological studies of parental smoking have indicated positive associations between paternal, rather than maternal, smoking and childhood cancer. This may be due to germ cell mutations in the father that develop before conception. Studies have not been able to show a significant association between EMF exposure and childhood cancer. It is probable that prenatal and postnatal exposure to low frequency EMFs through power lines or small appliances is not strongly associated with an increased risk of leukemia. No individual data has yet been collected to support or refute hypotheses involving the association between infectious agents and childhood cancer. The etiology of most cancers is unknown. The prenatal period is emerging as the etiologically relevant window for many childhood, particularly infant cancers. The association between maternal exposure to farm animals and development of brain tumors in children needs further research. Medical exposure to medications such as metronizadole in utero may be linked to childhood cancer. One study found an increased risk of neuroblastomas in children exposed to this drug in utero. Further studies may be needed given some outcomes may not appear until later in childhood or adolescence.

**Hypothesis #7: Exposure to solvents and paints may increase the risk of childhood cancers, including leukemia and brain tumors.*****General Information Related to Hypothesis #7***

- **Findings from recent research (targeted search):** Information reported in the following two studies contributed to the above-mentioned hypothesis.

Study #1: Colt JS, Aaron B. Parental occupational exposures and risk of childhood cancer. *Environmental Health Perspectives* 1998;106:909-925.

Study #1 hypothesis being tested: Paternal occupational exposure to solvents, paints, and motor vehicles may cause cancer in offspring.

Study #1 findings: The study found that evidence for an association between childhood leukemia and paternal exposure to solvents is strong; elevated risk was found between diverse occupations related to motor vehicles or involving exposure to exhaust gases and childhood leukemia; and results on the relationship between paternal exposure to ionizing radiation and childhood leukemia/lymphoma have varied. The authors state that assessing exposures to specific workplace agents is problematic when the only available information is a job or industry title, as is the case with most studies conducted to date. Workers with identical job titles can have different exposures depending on specific activity or task. Also, the timeframe of exposure is difficult to assess, i.e., whether exposure is prior to conception, during pregnancy, from exposure experienced at the workplace or from transfer of substances to the home, or after birth. Small numbers of exposed cases in studies of occupation and child cancer make it difficult to achieve stable results. Aggregating different jobs may increase numbers but also increase misclassification of exposures. Evidence from experimental investigations and epidemiologic studies of adult cancer and occupational exposure suggests that an association between fathers' occupations and the risk of childhood cancer is plausible. Furthermore, more research is needed on the association of childhood cancer and maternal occupations in textiles that use dyes, organic dusts and fibers, and EMF.

Study #2: Bowman P, Oblender M, Oeffinger KC, Ward J. Childhood cancer and environmental toxins: the debate continues. *Family & Community Health* 2002;24(4):27-38.\*

Study #2 hypothesis being tested: Exposure to environmental toxins and other risk factors (e.g., EMFs, radon, pesticides, solvents, parental occupational exposure, diet, ETS, alcohol, and infection during preconception, in utero, and postnatal periods) can lead to an increased risk of childhood cancers, particularly acute lymphocytic leukemia (ALL) and brain tumors.

Study #2 findings: Many environmental agents, including EMFs, radon, pesticides, solvents, parental occupational exposure, diet, ETS, alcohol, and infection, that are cited as causes of cancers such as leukemia, remain speculative. The authors suggest that childhood cancers are most likely a result of an interaction between genetic predisposition, environmental factors, and susceptibility. The authors call for further studies focused on genetic predisposition.

**Hypothesis #8: Exposure to insecticides/pesticides may increase the risk of childhood cancers, including leukemia and lymphomas.**

***General Information Related to Hypothesis #8***

- **Findings from recent research (targeted search):** Information reported in the following two studies contributed to the above-mentioned hypothesis.

Study #1: Meinert R, Schüz J, Kaletsch U, Kaatsch P, Michaelis J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. *American Journal of Epidemiology* 2000;151:639-646.

Study #1 hypothesis being tested: Exposure to insecticides used residentially, pesticides used on farms and gardens, and parental occupational pesticide exposure may be related to childhood cancer.

Study #1 findings: The study found an association between use of household insecticides and extermination of insects by professional pest controllers and lymphomas. Evidence of a link between pesticides and leukemia and lymphoma was weaker; the use of pesticides in gardens was not related to childhood leukemia and lymphoma, but use of pesticides on farms was weakly associated with childhood leukemia.

Study #2: Massey-Stokes M, Lanning B. Childhood cancer and environmental toxins: The debate continues. *Family & Community Health* 2002;24(4):27-38.+

Study #2 hypothesis being tested: Childhood cancers are linked to exposure to environmental toxins such as insecticides and pesticides.

Study #2 findings: The authors note that whether increases observed are truly due to cancer linked to environmental toxicant exposure or better diagnosis or more thorough reporting is unclear. Due to linkages between pesticides, diet, and insecticides, causes of childhood cancer are difficult to identify. Proving the causative nature of environmental toxins is difficult due to exposure estimation from personal memory recall or interview responses. Genetic susceptibility to some cancers has increased interest in biomarker research. However, except for families with a strong history of cancer, the strength of predictability with genetic biomarkers has been inconclusive.

**Hypothesis #9: Exposure to paternal/maternal smoking may increase the risk of childhood cancers, including brain tumors, and may increase the risk of lung cancer in adulthood.**

***General Information Related to Hypothesis #9***

- Primary central nervous system tumors are the leading cause of cancer related death among children less than 15 years of age. Such tumors account for approximately 20% of malignancies in this age group.<sup>31</sup>
- Cigarette smoking has been identified as a major source of preventable morbidity and premature mortality. Animal studies suggest that some effects of exposure in early life may not be apparent until adult life.<sup>32</sup>
- **Findings from recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Huncharek M, Kupelnick B, Klassen H. Paternal smoking during pregnancy and the risk of childhood brain tumors: Results of a meta-analysis. 2001;15:535-542.

Study #1 hypothesis being tested: Paternal smoking during pregnancy may be associated with increased risk of brain tumor development in the offspring.

Study #1 findings: A meta-analysis of numerous studies published in the literature - enrolling a total of 3,600 patients - demonstrated a statistically significant result suggesting an approximately 29% increased risk of brain tumor development associated with paternal smoking during pregnancy versus children of non-smoking fathers. Epidemiological data suggest that an association between paternal smoking during pregnancy and brain tumor development is biologically plausible. Transplacental migration of tobacco specific carcinogens to the fetus from ETS from the father's smoking during pregnancy poses a risk to the unborn child. However, the etiology of central nervous system tumors is yet unknown.

Study #2: Boffetta P, Tredaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. Environmental Health Perspectives 2000;108(1):73-82.

Study #2 hypothesis being tested: Childhood exposure to maternal smoking increases risks for childhood cancer and adult lung cancer.

Study #2 findings: Childhood exposure to maternal smoking increases risks for childhood cancer and adult lung cancer. Meta-analysis showed a 10% increased risk of childhood cancer as a result of exposure to maternal smoke. However, the increase in

<sup>31</sup> Huncharek M, Kupelnick B, Klassen H. Paternal smoking during pregnancy and the risk of childhood brain tumors: Results of a meta-analysis. 2001;15:535-542.

<sup>32</sup> Boffetta P, Tredaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. Environmental Health Perspectives 2000;108(1):73-82.

risk is small and may be explained by bias and confounding. In addition, studies have not shown a significant increased risk of adult lung cancer from exposure to passive smoking in childhood.

Study #3: Ross JA, Swensen AR. Prenatal epidemiology of pediatric tumors. *Current Oncology Reports* 2000 May;2(3):234-41.

*(Note: This study is cited under childhood cancers and other exposures – EMFs and infectious agents.)*

Study #3 hypothesis being tested: Infectious agents such as mycoplasma pneumonia and hepatitis A may lead to leukemia. There may be a dose-response relationship in the association between in utero exposure to radiation and childhood leukemia. Paternal smoking has a more powerful effect on childhood cancer than maternal smoking. EMF exposure may be associated with leukemia.

Study #3 findings: One study in Greece indicated that infants exposed in utero to radiation had a higher incidence of leukemia and that there was a positive dose-response relationship between incidence and radioactivity in the region. Most epidemiological studies of parental smoking have indicated positive associations between paternal, rather than maternal, smoking and childhood cancer. This may be due to germ cell mutations in the father that develop before conception. Studies have not been able to show a significant association between EMF exposure and childhood cancer. It is probable that prenatal and postnatal exposure to low frequency EMFs through power lines or small appliances is not strongly associated with an increased risk of leukemia. No individual data has yet been collected to support or refute hypotheses involving the association between infectious agents and childhood cancer. The etiology of most cancers is unknown. The prenatal period is emerging as the etiologically relevant window for many childhood, particularly infant, cancers. The association between maternal exposure to farm animals and development of brain tumors in children needs further research. Medical exposure to medications such as metronizadole in utero may be linked to childhood cancer. One study found an increased risk of neuroblastomas in children exposed to this drug in utero. Further studies may be needed given some outcomes may not appear until later in childhood or adolescence.

**Hypothesis #10: Exposure to infectious agents/viruses may increase the risk of childhood cancers, including brain tumors, and may increase the risk of lung cancer in adulthood.**

### ***General Information Related to Hypothesis #10***

- **Prevalence and incidence of brain tumors in children:** Brain tumors account for 20% of all childhood cancers. Between 1973 and 1994, incidence rates of childhood brain tumors (CBTs) increased 29%.<sup>33</sup>
- **Frequency/load of exposure to infectious agents:** Children of parents whose occupation is associated with higher exposure to animal viruses (e.g., veterinarians, farmers) may be at higher risk.<sup>34</sup>
- **Findings from recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Alexander FE. Clusters and clustering of childhood cancer: A review. *European Journal of Epidemiology* 1999;15(9):847-52.

Study #1 hypothesis being tested: Infectious processes may play a role in clustering of childhood cancer.

Study #1 findings: The authors note that despite data that suggests an infectious process associated with childhood leukemia, no definitive causative agent has been identified leading to childhood leukemia. Some studies have pointed to a possible infectious process leading to childhood leukemia and clustering of childhood cancer. No causal factor, however, has been identified that explains clustering. The authors suggest that, in order to explain cancer clusters, it will be helpful to identify causes of cancer through large national case-control studies and determine whether clustering is due to a single cause or due to chance aggregation of cases with separate causes.

Study #2: Yeni-Kmishian H, Holly EA. Childhood brain tumours and exposure to animals and farm life: a review. *Paediatric and Perinatal Epidemiology* 2000;14:248-256.

Study #2 hypothesis being tested: Fetal and/or childhood exposure to animal viruses through contact with farm animals and pets can induce brain tumor formation.

Study #2 findings: The authors found that out of five studies of childhood farm residence or exposure of mother or child to farm animals, four reported elevated risk for CBT. However, farm exposures are uncommon in the population studied and population attributable risks for CBT would be minimal. Small numbers of subjects in subgroups of exposed individuals provided inadequate power to rule out chance as a possible factor in most studies. Exposures on a farm are many and varied, and putative

<sup>33</sup> Yeni-Kmishian H, Holly EA. Childhood brain tumours and exposure to animals and farm life: a review. *Paediatric and Perinatal Epidemiology* 2000;14:248-256.

<sup>34</sup> Ibid.

elevated risk of CBT resulting from farm animal exposures could possibly be related to unmeasured pesticide exposure. Despite inconclusive evidence, the reported excess risk for CBT with maternal exposures to farm life is supported by parental occupational studies. Parental occupation in agriculture has been associated with other childhood cancers, such as leukemia. Also, veterinarians and farmers have significantly higher rates of brain tumors when compared with the general U.S. population. Farm residence and animal exposure place children at risk of contact with various viruses and parasites. Humans may be infected with animal viruses that may be related to brain tumorigenesis. An association between maternal or childhood exposure to neurocarcinogenic viruses from farm life and CBT needs further investigation.

Study #3: Ross JA, Swensen AR. Prenatal epidemiology of pediatric tumors. *Current Oncology Reports* 2000;2(3):234-41.

*(Note: This study is cited under childhood cancers and other exposures – EMFs and paternal/maternal smoking.)*

Study #3 hypothesis being tested: Infectious agents such as mycoplasma pneumonia and hepatitis A may lead to leukemia. There may be a dose-response relationship in the association between in utero exposure to radiation and childhood leukemia. Paternal smoking has a more powerful effect on childhood cancer than maternal smoking. EMF exposure may be associated with leukemia.

Study #3 findings: One study in Greece indicated that infants exposed in utero to radiation had a higher incidence of leukemia and that there was a positive dose-response relationship between incidence and radioactivity in the region. Most epidemiological studies of parental smoking have indicated positive associations between paternal, rather than maternal, smoking and childhood cancer. This may be due to germ cell mutations in the father that develop before conception. Studies have not been able to show a significant association between EMF exposure and childhood cancer. It is probable that prenatal and postnatal exposure to low frequency EMFs through power lines or small appliances is not strongly associated with an increased risk of leukemia. No individual data has yet been collected to support or refute hypotheses involving the association between infectious agents and childhood cancer. The etiology of most cancers is unknown. The prenatal period is emerging as the etiologically relevant window for many childhood, particularly infant cancers. The association between maternal exposure to farm animals and development of brain tumors in children needs further research. Medical exposure to medications such as metronidazole in utero may be linked to childhood cancer. One study found an increased risk of neuroblastomas in children exposed to this drug in utero. Further studies may be needed given some outcomes may not appear until later in childhood or adolescence.

## **Targeted Research Area: Endocrine Disrupters**

### **General Information on Endocrine Disrupters**

- **Prevalence and incidence of Endocrine Disrupters:**
  - Surveillance studies show an increasing incidence in potentially hormone-related conditions (hypospadias, cryptorchidism, testicular cancer, prostate cancer) in Canada and the U.S.<sup>35</sup>
  - In 1996, the U.S. EPA identified endocrine disruption as an environmental health problem. The incidence of testicular cancer has increased in almost all countries with reliable cancer registries.<sup>36</sup>
  - The incidence of endometriosis has been increasing over the past 25 years in developing countries. Hypospadias is one of the most common congenital anomalies. Data from five European countries and two U.S. surveillance systems reported unexplained increases in the rate of hypospadias from 1968 to 1993.<sup>37</sup>
- **Mortality from Endocrine Disrupters:** This information was not readily available to Lewin.
- **Disease severity/disease burden:** Endometriosis accounts for one-half million hospital bed-days in the U.S. (1980).<sup>38</sup>
- **Cost to individual/family/society/healthcare system :** This information was not readily available to Lewin.
- **Frequency/load of exposure:** This information was not readily available to Lewin.
  - Humans are exposed to endocrine disrupters through various routes (food, air, water, soil, pesticides, etc.). Neonatal exposures to phytochemicals occurs through bovine milk, and soy-based milk substitutes contain even greater amounts. The plasma concentration of genistein in infants soy-based formulas was, on average, 200 times greater than measured in infant-fed cow's milk formula and 300 times greater than in human breast milk.<sup>39</sup>
- **Special Populations:** Although many have been banned in the U.S., chemicals that have been identified as having endocrine-like activity still exist in many countries, and most persist for a long time in the environment. The south Atlantic region of the U.S. has the highest overall environmental levels of 54 toxic substances, including PCBs and dioxins.<sup>40</sup>

*Hypothesis #11, described on the following pages, is associated with the Endocrine Disrupters targeted research area.*

<sup>35</sup> Solomon GM, Schettler T. Environment and health: 6. Endocrine disruption and potential human health implications. Canadian Medical Association Journal 2000 Nov 28;163(11):1471-6.

<sup>36</sup> Weber RFA, Pierik FH, Dohle GR, Burdorf A. Environmental influences on male reproduction. BJU International 2002;89(2):143-148.

<sup>37</sup> Rubin CH, Niskar AS. Endocrine disruptors: an emerging environmental health problem. Journal of the Medical Association of Georgia 1999 Dec;88(4):27-30.

<sup>38</sup> Ibid.

<sup>39</sup> Akingbemi BT, Hardy MP. Oestrogenic and antiandrogenic chemicals in the environment: effects on male reproductive health. Annals of Medicine 2001;33(6):391-403.

<sup>40</sup> Rubin CH, Niskar AS. Endocrine disruptors: an emerging environmental health problem. Journal of the Medical Association of Georgia 1999 Dec;88(4):27-30.

**Hypothesis #11: Increased fetal exposure to endocrine disrupters may result in reproductive and physiological abnormalities.*****General Information Related to Hypothesis #11***

- **Findings from the recent research (targeted search):** Information reported in the following four studies contributed to the above-mentioned hypothesis.

Study #1: Eskenazi B, Bradman A, Castoria R. Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environmental Health Perspectives* 1999;107(3):409-419.

Study #1 hypothesis being tested: A higher incidence of urogenital abnormalities among male newborns and decline in qualitatively normal sperm may be due to a disruption of reproductive development caused by endocrine disrupters.

Study #1 findings: There is evidence that humans have been exposed to endocrine disrupters present in the environment. Significant levels of endocrine disrupters have been detected in human tissues and have been associated with developmental and reproductive anomalies in laboratory species. Urogenital anomalies in newborns, testicular cancer, and impaired sperm viability may be a result of the effect of exogenous endocrine disrupters. In addition to an oral route, investigation of the effects of dermal and inhalation exposure are also required. However, no direct evidence currently shows that endocrine disrupters in the environment affect humans.

Study #2: Rubin CH, Niskar AS. Endocrine disrupters: an emerging environmental health problem. *Journal of the Medical Association of Georgia* 1999;88(4):27-30.

Study #2 hypothesis being tested: Accumulation of an endocrine disrupter in the environment can cause adverse health effects, including birth defects, cancer, impaired fertility, and developmental disabilities.

Study #2 findings: Although clinical use of exogenous estrogens has been associated with impaired fertility, e.g., endometriosis, studies have not conclusively shown an association in humans. Hormone-like chemicals (PCBs and dioxins) in the environment may be responsible for some of the increased incidence of endometriosis. Hypospadias, the abnormal placement of the urethral opening on the penile shaft, is influenced by in utero hormonal levels and may be associated with human exposure to environmental chemicals that interfere with normal testosterone activity.

Study #3: Solomon GM, Schettler T. Environment and health: 6. Endocrine disruption and potential human health implications. *Canadian Medical Association Journal* 2000;163(11):1471-6.

Study #3 hypothesis being tested: There is an association between occupational exposure to solvents or pesticides and adverse effects on offspring such as hypospadias or cryptorchidism.

Study #3 findings: Studies in humans and laboratory animals have found associations between exposure to specific pesticides or chemicals and levels of thyroid stimulating hormone and abnormal sexual behavior or feminization of males. However, population-based epidemiologic studies relevant to endocrine disruption are still few and limited by the time lag between exposure and clinical disease, difficulty of defining exposure and control populations, poor retrospective assessment of exposures during the prenatal period. Also a clearer understanding of gene-environment interactions is needed. Opinions of researchers vary whether endocrine disrupters at current exposure levels affect human health or if suggestive evidence is enough to call for increased action to shield from endocrine disrupters.

Study #4: Weber RFA, Pierik FH, Dohle GR, Burdorf A. Environmental influences on male reproduction. *BJU International* 2002;89(2):143-148.

Study #4 hypothesis being tested: The increasing incidence of reproductive abnormalities (poor semen quality, hypospadias, testicular cancer) in males may be related to increased estrogen exposure in utero. Increased exposure to endocrine disrupters during fetal life may disrupt development of testis and the rest of the male reproductive tract.

Study #4 findings: Findings are inconclusive due to insufficient human studies with controlled comparisons, especially with all-male populations. With regard to declining sperm quality, most study populations reviewed cannot be regarded as representative of the normal population. Furthermore, other complicating factors (illnesses, variation in scrotal temperature due to clothing) are not addressed in studies. Sufficient evidence exists that reproductive disruption in wildlife may be caused by environmental pollutants, specifically by endocrine-disrupting compounds; however, only circumstantial evidence exists for most compounds.

## **Targeted Research Area: Environmental Toxicants**

### **General Information on Environmental Toxicants**

- **Prevalence and incidence of diseases associated with environmental toxicants:**
  - Reported rates of asthma, developmental disorders, and cancer in children have increased in the past decades. Although improved detection and reporting have contributed to these observed increases, environmental factors play a role. Reported rates of ADHD, learning disabilities, and autism have markedly increased in the U.S. in the last decade.<sup>41</sup> Approximately 17% (12 million) of U.S. children (<18 years of age) have one or more developmental disabilities; 3-6% are affected by ADHD; 5-10% are affected by learning disabilities. Incidence of autism may be as high as 2/1,000.
  - Rates of these diseases are disproportionately high in underserved, minority populations in low-income communities.<sup>42</sup>
  - As many as 28% of all neurodevelopmental disabilities in children are of environmental origin. There has been increasing incidence in conditions thought to be caused by endocrine disruptors. There has been increasing incidence in pediatric cancers; glioma, the second most common malignancy in children, has increased in incidence by close to 40% since 1972.<sup>43</sup>
- **Mortality from environmental toxicants:** Mortality rates vary depending on the toxicant exposure and associated disease outcome.
- **Disease severity/disease burden:** Disease severity or burden varies depending on the disease outcome.
- **Cost to individual/family/society/healthcare system:** Cost varies depending on the disease outcome.
- **Frequency/load of exposure to environmental toxicants:**
  - Children's exposure and susceptibility to environmental toxicants vary with their developmental stage.<sup>44</sup>
  - The frequency of exposure to environmental toxicants is dependent on the physiologic characteristics, behavioral patterns, and developmental stages of children.<sup>45</sup>
  - An estimated 25,000 children are poisoned by pesticides each year.<sup>46</sup>

<sup>41</sup> Perera FP, Illman SM, Kinney PL, Whyatt RM, Kelvin EA, Shepard P, et al. The challenge of preventing environmentally related disease in young children: community-based research in New York City. *Environmental Health Perspectives* 2002;110(2):197-204.

<sup>42</sup> Ibid.

<sup>43</sup> Landrigan PJ. Children's environmental health. Lessons from the past and prospects for the future. *Pediatric Clinics of North America* 2001;48(5):1319-30.

<sup>44</sup> Gitterman BA, Bearer CF. A developmental approach to pediatric environmental health. *Pediatric Clinics of North America* 2001;48(5):1071-83.

<sup>45</sup> Hubal EAC, Sheldon LS, Burke JM, McCurdy TR, Berry MR, Rigas ML, et al. Children's exposure assessment: a review of factors influencing children's exposure, and the data available to characterize and assess that exposure. *Environmental Health Perspectives* 2000; 108(6):475-86.

<sup>46</sup> Centers for Disease Control and Prevention. *The Children's Environmental Health Report Card*. Available at: [http://www.cdc.gov/nceh/asthma\\_old/factsheets/reportcard.htm](http://www.cdc.gov/nceh/asthma_old/factsheets/reportcard.htm)

- **Special populations:** This information was not readily available to The Lewin Group.

*Hypotheses 12 - 14, described on the following pages, are associated with the Environmental Toxicants targeted research area.*

**Hypothesis #12: Exposure to contaminants in water, such as chlorine disinfection byproducts, can lead to adverse birth outcomes such as neural tube defects, low birth weight, and spontaneous abortions.**

***General Information Related to Hypothesis #12***

- **Frequency/load of exposure to contaminants in water:**
  - 85% of all homes in the U.S. receive their water from public water systems. Most of these systems use chlorine for disinfection, leading to exposure to potentially harmful chlorination disinfection by-products.<sup>47</sup>
  - Exposure to disinfection byproducts (DBPs) is likely to be misclassified due to a variety of factors, including variability in water consumption, seasonal variability in DBP formation, and exposure to other sources of DBPs.<sup>48</sup>
- **Findings from recent research (targeted search):** Information reported in the following two studies contributed to the above-mentioned hypothesis.

Study #1: Bove F, Shim Y, Zeitz P. Drinking water contaminants and adverse pregnancy outcomes: a review. *Environmental Health Perspectives* 2002;110:61-74.

Study #1 hypothesis being tested: Drinking water contaminants (e.g., chlorination disinfection byproducts) are associated with adverse pregnancy outcomes.

Study #1 findings: Moderate evidence from studies of trihalomethanes, a type of chlorination disinfection by-product present in drinking water, have shown an association with small for gestational age (SGA) infants, neural tube defects, and spontaneous abortions. The authors suggest the association between water contaminants, and chlorinated solvents in particular, and adverse birth outcomes be included in a national longitudinal study tracking the prenatal through adolescent periods.

Study #2: Zender R, Bachand AM, Reif JS. Exposure to tap water during pregnancy. *Journal of Exposure Analysis and Environmental Epidemiology* 2001;11(3):224-30.

Study #2 hypothesis being tested: Exposure to disinfection byproducts (DBP), which is associated with adverse reproductive outcomes, is likely to be misclassified. (Please note: this article focuses on the exposure, rather than the disease area.)

Study #2 findings: Misclassification of exposure in studies of DBPs and reproductive outcomes is likely to arise from several sources including residential mobility during pregnancy, use of private wells rather than municipal system, individual variability in daily water consumption, seasonal variability in DBP formation and spatial

<sup>47</sup> Bove F, Shim Y, Zeitz P. Drinking water contaminants and adverse pregnancy outcomes: a review. *Environmental Health Perspectives* 2002;110:61-74.

<sup>48</sup> Zender R, Bachand AM, Reif JS. Exposure to tap water during pregnancy. *Journal of Exposure Analysis and Environmental Epidemiology* 2001;11(3):224-30.

concentrations of DBPs within the distribution system. In addition, failure to account for dermal and inhalation exposures to DBPs is likely to lead to an underestimate of total exposure. Study results heighten concern about DBP exposure estimates as individual differences in water consumption must be taken into account when assessing exposure to DBPs.

**Hypothesis #13: Exposure to environmental toxicants, such as air pollutants and DEHP (di-2-ethylhexyl phthalate), can affect various stages of child development, from intrauterine to postnatal development.**

***General Information Related to Hypothesis #13***

- **Frequency/load of exposure to DEHP:** The average total daily individual ambient exposure to DEHP in the U.S. is estimated to be 0.27 mg per day, excluding workplace air exposures, and indoor air exposures from off-gassing of building materials. Daily exposures in the medical setting may be three times the magnitude of exposure in the general population. Medical devices contain 30-40% DEHP by weight. The degree of leaching from a medical device can be as much as 10-15% of the available DEHP in the device. Newborns receive among the highest doses of DEHP from blood transfusions, extracorporeal membrane oxygenation, and respiratory therapy. DEHP can also cross the placenta, exposing the fetus.<sup>49</sup>
- **Findings from recent research (targeted search):** Information reported in the following four studies contributed to the above-mentioned hypothesis.

Study #1: Pereira LAA, Loomis D, Conceicao GMS, Braga ALF, Arcas RM, Kishi HS, et al. Association between air pollution and intrauterine mortality in Sao Paulo, Brazil. *Environmental Health Perspectives* 1998;106(6):325-329.

Study #1 hypothesis being tested: There is an association between intrauterine mortality and air pollution.

Study #1 findings: The study showed that the association was strong between intrauterine mortality and air pollution for NO<sub>2</sub>, but less for SO<sub>2</sub> and CO. The association was stronger when all three pollutants were considered together. The study results showed a significant association between air pollution and intrauterine mortality in San Paulo for the period January 1991 to December 1992. The authors state that there have been few studies on the susceptibility to air pollution and the possible effects of air pollution on fetuses.

Study #2: Gitterman BA, Bearer CF. A developmental approach to pediatric environmental health. *Pediatric Clinics of North America* 2001;48(5):1071-83.

Study #2 hypothesis being tested: Children's exposure and susceptibility to environmental toxicants vary with their developmental stage.

Study #2 findings: There are differences in exposures, pathways of absorption, tissue distribution, ability to bio-transform or eliminate chemicals from the body, and responses to chemical and radiation. The differences vary with each developmental

<sup>49</sup> Tickner JA, Schettler T, Guidotti T, McCally M, Rossi M. Health risks posed by use of Di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review. *American Journal of Industrial Medicine* 2001;39(1):100-11.

stage of the child. Children respond differently to environmental toxicants than adults and thus cannot be considered "little adults" in the field of environmental medicine.

Study #3: Tickner JA, Schettler T, Guidotti T, McCally M, Rossi M. Health risks posed by use of di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review. *American Journal of Industrial Medicine* 2001;39(1):100-11.

Study #3 hypothesis being tested: Di-ethylhexyl phthalate (DEHP) exposure from medical care materials may have adverse health effects in certain groups of patients, particularly developing fetuses and neonates.

Study #3 findings: Sufficient toxicological data are readily available to cause concern about exposure to fetus, neonate, infant, child, or chronically ill. Due to the variability of toxicity of DEHP in multiple organs, the variability in human exposure and susceptibility to effects and uncertainties in extrapolating animal data to humans, estimates of human risk or safe levels of exposure cannot be established at this time. Epidemiological studies of DEHP-exposed humans are not available. The authors note that due to limitations of current data, further research should be conducted to better understand and characterize DEHP.

Study #4: Hubal EAC, Sheldon LS, Burke JM, McCurdy TR, Berry MR, Rigas ML, et al. Children's exposure assessment: a review of factors influencing children's exposure, and the data available to characterize and assess that exposure. *Environmental Health Perspectives* 2000; 108(6):475-86.

Study #4 hypothesis being tested: Physiologic characteristics, physical activities, dietary habits, sex, socioeconomic status (SES) and race/ethnicity of children all influence children's exposures to environmental contaminants. (Please note: this article focuses on the exposure, rather than the disease area.)

Study #4 findings: Physiologic characteristics affect a child's rate of contact and exposure by affecting exposure uptake. Infants have a surface area-to-body ratio twice as great than that of adults. Diets of infants and children are usually very limited and may increase their exposure to environmental contaminants such as pesticide residues in fruit. Gender affects activity levels and behavior of children and may account for variance in type of exposures encountered. The authors state that data are insufficient to characterize a relationship between SES, ethnicity/race, age and environmental exposure. Improvements need to be made to data collection efforts. The authors call for more research on the identification of appropriate benchmarks for categorizing children in exposure assessments (e.g., according to when developmental changes occur), development and improvement of methods for monitoring exposures and activities, and collection of physical activity data for children to assess exposure by all routes.

**Hypothesis #14: Exposure to environmental toxicants such as pesticides (e.g., organophosphates) can play a causal role in childhood diseases ranging from asthma to neurological disorders.**

***General Information Related to Hypothesis #14***

- **Exposure to environmental toxicants:**
  - 34.5 million kg (76 million lbs) of active pesticide ingredients were used in home and garden settings, according to most recent EPA estimate (1997).<sup>50</sup>
  - One report suggested that during the period of 1997-99, organophosphates was one class of pesticide that most likely caused illness or death in U.S. children. Exposures to this pesticide totaled 40,090 over this time period. Moderate or severe morbidity from exposure to organophosphates totaled 1,994 patients from 1997-99. Twenty-one deaths were related to exposure to this class of pesticide over the same period of time.<sup>51</sup>
  - Children are at risk for exposure to 2,800 high-production-volume (HPV) chemicals that are produced in quantities of more than 1 million tons per year. These HPV chemicals are distributed widely in the environment. Only 43% of HPV chemicals have been tested for their potential to cause toxicity; fewer than 20% have been tested for their ability to interfere in child development.<sup>52</sup>
- **Findings from recent research (targeted search):** Information reported in the following study contributed to the above-mentioned hypothesis.

Study #1: Perera FP, Illman SM, Kinney PL, Whyatt RM, Kelvin EA, Shepard P, et al. The challenge of preventing environmentally related disease in young children: community-based research in New York City. *Environmental Health Perspectives* 2002;110(2):197-204. (Note: This study is also cited under the research areas of asthma, childhood cancer, and neurodevelopmental disorders.)

Study #1 Hypothesis being tested: Prenatal and postnatal exposure to environmental toxicants can lead to respiratory disease, impaired neurological development, genetic damage, and increased risk of cancer.

Study #1 Findings: Environmental toxicants can modify the formation and maturation of the lungs. In utero sensitization to specific allergens can occur independently of maternal sensitization, putting children at higher risk for asthma. Neurochemical and behavioral effects arise from exposure to toxicants during critical windows of fetal development. Fetuses also clear toxicants less efficiently than adults and are more vulnerable to genetic damage and subsequent risk of cancer. Nutritional deficits in maternal diet have been linked to development of asthma in the child. Gene-environment interactions and psychosocial factors can also make a fetus or newborn

<sup>50</sup> Reigart JR, Roberts JR. Pesticides in children. *Pediatric Clinics of North America* 2001;46(5):1185-98.

<sup>51</sup> Ibid.

<sup>52</sup> Landrigan PJ. Children's environmental health. Lessons from the past and prospects for the future. *Pediatric Clinics of North America* 2001;48(5):1319-30.

more susceptible to disease. Some studies suggest that women who live in violent, crime-ridden neighborhoods experience pregnancy complications and adverse birth outcomes. Prenatal and postnatal exposure to environmental toxicants can lead to respiratory disease, impaired neurological development, genetic damage, and increased risk of cancer. Nutrition, gene-environment interaction, and psychosocial stressors are cofactors that compound the susceptibility of the fetus and newborn.

## **Targeted Research Area: Injury**

### **General Information on Injury**

- **Prevalence and incidence of injury:**
  - Unintentional injuries claim the lives of more children each year than any other cause of death. At least one adolescent between ages 10 and 19 years dies of an injury every hour of every day. Injuries kill more adolescents than all diseases combined. Annually, 20-25% of all children sustain an injury sufficiently severe to require medical attention, missed school or bed rest.<sup>53</sup>
  - Fatal injuries accounted for 61.6% of deaths from age 1 through 19; in 1998, a total of 16,349 children aged 1 through 19 died from injuries.<sup>54</sup>
  - The true incidence of fatalities due to problems within the family is thought to be higher than the recorded 1,200 to 1,500 cases per year, with estimates ranging from 2,000 to 5,000 per year. Maltreatment of children causes an estimated 2,000 deaths annually in the US; 90% of these occur among children less than 5 years of age, making maltreatment the leading cause of injury fatality in this age group.
  - Each year in the U.S., 200,000 preschool and elementary school children visit the emergency department (ED) for injuries sustained on playground equipment (about 1 injury every 2.5 minutes).<sup>55</sup>
- **Mortality from Injury:** This information was not readily available to Lewin.
- **Disease severity/disease burden:** This information was not readily available to Lewin.
- **Cost to individual/family/society/healthcare system:** According to the Department of Transportation, in 1993, the economic costs of injury, disability, and death of children were well over \$16B in the U.S. In a report by Miller et al. (2000), the estimated lifetime resource and productivity cost of unintentional injuries to children ages 0 to 19 in 1996 was \$81B. The bulk of the financial burden associated with childhood unintentional injuries results from work losses experienced by injured children and their caregivers. Injury, vascular disease, and cancer account for similar proportions of medical spending, however, research funding in injury prevention is significantly less than for cancer (approximately 2.5% to 10.5%).<sup>56</sup>
- **Frequency/load of exposure:**
  - Reports of fatal child abuse and neglect as well as child homicide rates are rising. Very young children and adolescents are at highest risk for childhood injury, and

<sup>53</sup> Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. *Facts on Adolescent Injury*. Available at <http://www.cdc.gov/ncipc/factsheets/adoles.htm>

<sup>54</sup> Stoddard FJ, Saxe G. Ten-year research review of physical injuries. *Journal of the American Academy of Child and Adolescent Psychiatry* 2001;40(10): 1128-1145.

<sup>55</sup> Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. *Unintentional Injury Prevention*. Available at <http://www.cdc.gov/ncipc/duip/duip.htm>

<sup>56</sup> Miller TR, Romano EO, Spicer RS. The cost of childhood unintentional injuries and the value of prevention. *The Future of Children* 2000;10:137-163.

- typically, sports, falls, motor-vehicle traffic injuries, and burns are the common causes.
- According to a 1995 General Accounting Office study described by Cummins et al., 14 million students attend schools and child care settings with substandard structural conditions; approximately one-third of schools need extensive repair or replacement. Low-income children are more likely to be exposed to structural hazards. Among poor children, African-American children are more likely to live in substandard housing conditions than are white children.
- **Special Populations:** This information was not readily available to Lewin.

*Hypotheses 15 – 18, described on the following pages, are associated with the Injury targeted research area.*

**Hypothesis #15:** Factors in the immediate environment surrounding children (e.g., instability in the home, household composition), can be major risk factors in the incidence of childhood injury.

### ***General Information Related to Hypothesis #15***

- **Findings from the recent research (targeted search):** Information reported in the following two studies contributed to the above-mentioned hypothesis.

Study #1: Stiffman MN, Schnitzer PG, Adam P, Kruse RL, Ewigman BG. Household composition and risk of fatal child maltreatment. *Pediatrics* 2002;109:615-621.

Study #1 hypothesis being tested: Household composition, i.e., people living in the child's household at the time of death and their relationships to the child, may be a risk factor for fatal child maltreatment.

Study #1 findings: Children residing in households with adults unrelated to them had the highest risk of maltreatment-related death. Children are at higher risk for maltreatment injury if residing in households with an unrelated adult, primarily an adult male. Two key risk factors are living with a stepfather or the mother's boyfriend. However, the reason children were more likely to die from maltreatment if an unrelated adult resided in the household is not clear; other household composition factors and risk factors are likely to combine to affect morbidity and mortality. The authors hypothesize that the presence of an unrelated adult in the home is a marker for instability in the household or that unrelated adults are not as keenly involved in protecting children from harm as are their biological parents.

Study #2: Stoddard FJ, Saxe G. Ten-year research review of physical injuries. *Journal of the American Academy of Child and Adolescent Psychiatry* 2001;40(10):1128-1145.

Study #2 hypothesis being tested: Children who are raised in chaotic and disorganized households may be at higher risk for physical and psychiatric injury from maltreatment that includes physical abuse, sexual abuse, and neglect. These children are likely to develop psychiatric problems resulting from self-blame or lack of trust in others.

Study #2 findings: This review of the past ten years of research (relevant to psychiatry) on injuries in children and adolescents reports that neglect accounts for more injuries and deaths than does physical abuse, although filings for both have increased steadily (660,000 in 1976 to 3.0 million in 1995). Studies have focused on specific populations with different types of neglect or abuse. Children in the age range of 1 to 5 years are at high risk for burn injuries, and according to Renz and Sherman (1993) and Yeoh et al (1994), injuries due to neglect or abuse range from 5.9% to 26% of pediatric burn admissions. Once injury occurs, children develop self-blame, lack of trust in others, and difficulty regulating affect. It is likely that disorganized and chaotic families lack the capacity to assist children in the physical and psychological recovery from injury. Family foster care, where neglect and abuse has been reported to occur, should also be assessed as potential settings for child maltreatment.

**Hypothesis #16:** Children who are exposed to physical and psychological stress due to large disruptions in their broader community/social environment, such as war, natural disasters (e.g., hurricanes, bombings, large-scale accidents such as crashes), and poverty may be at high risk for developing complex psychological problems (in addition to physical injuries) due to deaths in the family, home damage, and displacement.

***General Information Related to Hypothesis #16***

- **Findings from the recent research (targeted search):** Information reported in the following study contributed to the above-mentioned hypothesis.

Study #1: Stoddard FJ, Saxe G. Ten-year research review of physical injuries. Journal of the American Academy of Child and Adolescent Psychiatry 2001;40(10):1128-1145.

Study #1 hypothesis being tested: Children who reside in societies or communities exposed to problems such as poverty, damage from natural disasters, large accidents and wars, may be at high risk for injuries with adverse psychiatric outcomes.

Study #1 findings: Due to ongoing disruption in the child's social environment, children exposed to poverty, extreme environmental disruption, or wars develop PTSD. Furthermore, lack of community and individual help from parents or guardians during stressful periods precludes children from gaining access to appropriate medical attention or care when injury has occurred. Injuries sustained in large disasters or wars leads to more pervasive psychiatric responses due to inevitable and continuous disruption in the environment.

**Hypothesis #17:** As children grow and spend more time in the exterior environment, they are exposed to factors in the modern built environment that place them at risk for injury and death. The quality and structural safety of buildings, traffic, and play areas may affect the chance of incurring illness, disability, or injury. Poor construction and structural hazards may be leading causes for the prevalence of childhood falls, burnings, drownings, and secondary harms and diseases.

***General Information Related to Hypothesis #17***

- **Findings from the recent research (targeted search):** Information reported in the following two studies contributed to the above-mentioned hypothesis.

Study #1: Bartlett S. The problem of children's injuries in low-income countries: A review. *Health Policy and Planning* 2002;17:1-13.

Study #1 hypothesis being tested: Children in low-income communities and countries are at higher risk for unintentional injuries. Factors such as challenging living conditions, heavy traffic, lack of safe play space, and absence of child care options, which are prominent characteristics in low-income settings, may place children at high risk for preventable injury-related deaths.

Study #1 findings: Based on data from the WHO, UNICEF, and various other studies, injury rates for low-income countries are five times higher than those in higher-income countries. Children in poverty are more often victims of injuries due to risk factors in their surrounding built environment (e.g., poorly constructed playgrounds, overcrowded homes, unprotected machinery in homes). Children in low-income settings are more likely to be hospitalized due to burns, drownings, falls, traffic accidents, etc. According to this review, child injuries are considered a minor issue in low-income countries relative to the burden imposed by communicable disease and malnutrition, although they are the cause of death and disability for millions of children each year.

Study #2: Cummins SK, Jackson RJ. The built environment and children's health. *Children's Environmental Health* 2001;48:1241-1252.

Study #2 hypothesis being tested: The quality and design of a child's physical environment are associated with rates of injury and disability. Risk factors in the built environment surrounding children, such as poor-quality housing, poor traffic safety, and degradation of structures, may be associated with pediatric injuries.

Study #2 findings: Studies performed in inner-cities and studies on the structural condition of schools and child care settings conducted by the General Accounting Office showed that faulty construction or neglected maintenance places children at increased risk for falls, burns, and other injuries. The authors report that 40% of fall fatalities in 1991 occurred in children less than 5 years of age due to falls from buildings. In New York City, window barriers were a highly effective method of preventing toddler falls from windows. The authors highlight faulty construction or neglected maintenance as primary causes of structural hazards in homes and schools. Building defects are likely to increase the incidence of structural hazards and fires. Inadequate or deferred property maintenance, which is common in low-income properties, can also lead to structural damage, inadequate heating or lighting and electrical hazards. Exposures to overgrowth of mold, hazardous materials that contain lead or asbestos, infestation of rodents and insects, and poor air quality have been linked to asthma, injury from burns or falls, and carbon monoxide poisoning in children.

**Hypothesis #18:** Children may be at high risk for injury due to psychosocial factors in environments outside the home. Children who experience psychosocial stress in schools may be prone to aggressive or violent behavior, resulting in unintentional and/or intentional injury to oneself and others. School environments that exhibit high rates of psychosocial problems may also exhibit high rates of sports-related injuries among children and physical violence between children.

***General Information Related to Hypothesis #18***

- **Findings from the recent research (targeted search):** Information reported in the following study contributed to the above-mentioned hypothesis.

Study #1: Laflamme L, Menckel E. Pupil injury risks as a function of physical and psychosocial environmental problems experienced at school. *Injury Prevention* 2001;2:146-9.

Study #1 hypothesis being tested: Physical and psychosocial environmental problems experienced at school are associated with injury risk.

Study #1 findings: Among schools that were enrolled in the study conducted in Sweden, schools with psychosocial problems in the study had more than twice as many injuries due to violence than expected by chance, more injuries during sports activities, and more injuries of all kinds. Schools were categorized as having 'psychosocial problems' according to responses given to questionnaires about pupils' work environments. The schools reporting psychosocial problems had more injuries than by chance when considering sports related injuries (i.e., incurred during school gymnastics or sports), injuries due to physical violence (i.e., due to acts of physical violence between pupils), and all injuries aggregated. The study points to psychosocial problems that children encounter in the school environment as exacerbating factors for intentional or unintentional injuries among pupils.

## ***Targeted Research Area: Neurodevelopment & Biobehavioral Development***

### ***General Information on Neurodevelopment & Biobehavioral Development***

- **Prevalence and incidence of disorders related to Neurodevelopment:** & Biobehavioral Development
  - Approximately 1% of all children are mentally retarded.
  - Estimated that nearly 12 million children in the United States under age 18 suffer from one or more learning, developmental, or behavioral disabilities.<sup>57</sup>
  - Attention deficit hyperactivity disorder (ADHD) affects 3%-6% of all school children, though recent evidence suggests prevalence as high as 17%. Children taking Ritalin for ADHD has doubled every 4-7 years since 1971; an estimated 1.5 children are on Ritalin.<sup>58</sup>
  - Learning disabilities affect an estimated 5-10% of children in public schools.<sup>59</sup>
- **Mortality from Neurodevelopment and Biobehavioral Development Disorders:** This information was not readily available to Lewin.
- **Disease severity/disease burden:** Though trivial on an individual level, when applied across populations, neurotoxicants have a significant impact. A loss of 5 points in IQ is of minimal significance in a person with an average IQ. However, a shift of 5 IQ points in the average IQ of a population of 260 million increases the number of functionally disabled by over 50% (from 6 to 9.4 million).<sup>60</sup>
- **Cost to individual/family/society/healthcare system** Evokes broader questions about career and educational opportunities and how effects of toxicology can affect social class. Societal and economic benefits are considerable as there can be reductions in poverty, welfare, crime, and high school dropouts, and increases in earnings.<sup>61</sup>
- **Frequency/load of exposure:** This information was not readily available to Lewin.
- **Special Populations:** This information was not readily available to Lewin.

*Hypotheses 19 – 27, described on the following pages, are associated with the Neurodevelopment and Biobehavioral Development targeted research area.*

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<sup>57</sup> Schettler T, Stein J, Reich F, et al. In harms way: Toxic threats to child development. Greater Boston Physicians for Social Responsibility 2000.

<sup>58</sup> Ibid.

<sup>59</sup> Ibid.

<sup>60</sup> Ibid.

<sup>61</sup> Weiss B. Vulnerability of children and the developing brain to neurotoxic hazards. Environmental Health Perspectives 2000;108:375-81.

**Hypothesis #19:** Organophosphate pesticides such as PCBs, PCDDs, and PCDFs have a detrimental impact on neurodevelopment, causing functional, neurologic, and cognitive expression.

***General Information Related to Hypothesis #19***

- **Frequency/load of exposure:**
  - Exposure to organic contaminants begins prior to conception and continues throughout gestation. However, human newborns are exposed to larger amounts of organic contaminants through breast feeding than in any other stage of development or life.<sup>62</sup>
  - Exposure is universal due to the mode of exposure. PCBs do not biodegrade and thus accumulate in the food chain, and are present in fish, fish products, animal fats, and often pass from the mother to the fetus/newborn through the placenta or breast milk.<sup>63</sup>
  - Animal studies of lead, mercury, and PCBs each underestimate the levels of exposures that cause effects in humans by 100 to 10,000-fold.<sup>64</sup>
- **Findings from the recent research (targeted search):** Information reported in the following four studies contributed to the above-mentioned hypothesis.

Study #1: Eskenazi B, Bradman A, Castoria R. Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environmental Health Perspectives* 1999;107(3):409-419.

Study #1 hypothesis being tested: Low-level exposure to organophosphate pesticides has potential adverse health effects on children's nervous and respiratory systems.

Study #1 findings: Studying findings are inconclusive. Data neither support nor refute adverse health effects from low-level pesticide exposure. However, evidence available from animal models shows evidence of significant neurodevelopmental effects that link exposure to organophosphate pesticides during gestation and postnatal development to: 1) altered DNA synthesis in the brain, 2) adverse effects on cellular intermediates, 3) decreased motor function, and 4) low birth weight, which may be significant to the development of asthma or determining its severity. Additional research is needed to determine the various sources, pathways and levels of pesticide exposure in children, especially children living in high risk environments such as farms and agricultural communities, and develop effective interventions and minimize pesticide exposure. Additionally, more research is needed to understand whether pesticide exposure could be an important factor in the etiology and morbidity of childhood asthma.

<sup>62</sup> Feeley M, Brouwer A. Health risks to infants from exposure to PCBs, PCDDs and PCDFs. *Food Additives and Contaminants* 2000 Apr;17(4):325-33.

<sup>63</sup> Ribas-Fito N, Sala M, Kovgevinas M, Sunyer J. Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. *Journal of Epidemiology and Community Health* 2001; 55: 537-546.

<sup>64</sup> Schettler T, Stein J, Reich F, et al. In harms way: Toxic threats to child development. *Greater Boston Physicians for Social Responsibility* 2000.

Study #2: Feeley M, Brouwer A. Health risks to infants from exposure to PCBs, PCDDs and PCDFs. *Food Additives and Contaminants* 2000;17(4):325-33.

Study #2 hypothesis being tested: Environmental exposure to a variety of anthropogenic persistent organic chemicals, such as dioxins and PCBs, can cause adverse mental and physical developmental abnormalities.

Study #2 findings: Studies have found detectable concentrations of PCBs and dioxins in amniotic fluid, placenta, and fetal tissue, while breastfed infants were observed having higher levels of toxins in their blood than their mother. Infants exposed in utero were observed to have deficits to their mental and functional development (e.g., lower birth weights, alternations in thyroid hormones, lymphocyte subpopulations, and neurodevelopment). There were more negative effects for infants exposed in utero versus through breastfeeding. Though subtle, the observed neurodevelopment deficits can have unknown consequences related to future intellectual function. Efforts should focus on identification and control of environmental and food chain contamination since in utero exposure is a direct consequence of accumulated maternal body burdens prior to conception.

Study #3: Ribas-Fito N, Sala M, Kovgevinas M, Sunyer J. Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. *Journal of Epidemiology and Community Health* 2001;55:537-546.

Study #3 hypothesis being tested: Exposure to organochlorine compounds such as polychlorinated biphenyls hinder neurological development in children.

Study #3 findings: Studies evaluating exposed children showed increase in abnormal reflexes, decrease in motor skills, and deficits in cognitive skills. Review of studies indicates that prenatal exposure to PCBs has subtle adverse effects on child neurodevelopment. However, due to differences in study designs, the degrees of risk associated with neurodevelopmental effects at current levels of exposures (dose-response relation), critical periods of exposure, and the possible reversibility of effects are not established. Also, since exposure is universal, more research should be conducted on populations exposed to organochlorine compounds.

Study #4: Weiss B. Vulnerability of children and the developing brain to neurotoxic hazards. *Environmental Health Perspectives* 2000;108:375-81.

Study #4 hypothesis being tested: Neurobehavioral toxicity of a particular or group of agents can impair brain development and functional expression.

Study #4 findings: Lead is one of a multitude of toxic agents that impact IQ scores, additional factors include: maternal intelligence, family income, education, race, child's environment, etc.). Maternal smoking during pregnancy also lowers IQ of offspring.

**Hypothesis #20:** Autism is a neurodevelopmental disease that may be linked to components of vaccines and immunizations and may have a genetic link.

**General Information Related to Hypothesis #20**

- **Prevalence and incidence of autism:**
  - The prevalence of autism estimates run from approximately 1-in-500 children, to 2-in-1000 children.<sup>65,66</sup>
  - Autism spectrum disorders have increased from 1 in 10,000 in 1978 to 1 in 300 in 1999.<sup>67</sup>
  - Though not as prevalent as other developmental disorders, autism spectrum disorders affect more than 400,000 people in the U.S. The reported number of autism cases is increasing dramatically every year.<sup>68</sup>
  - Within the state of California, the number of children entered into the autism registry increased by 210% between 1987 and 1998.<sup>69</sup>
- **Disease severity/disease burden**
  - Autism is a complex, life-long biological disorder of development that results in social interaction problems, communication difficulties, and restrictive or repetitive interests and behaviors.<sup>70</sup>
  - Autism is one of the most severe developmental brain disorders.<sup>71</sup>
- **Special Populations:** Males are three-to-four times more likely to be affected by autism than females; it occurs in all racial, ethnic, and social groups.<sup>72</sup>
- **Findings from the recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Megson MN. Is autism a G-protein defect reversible with natural vitamin A? *Medical Hypotheses* 2000;54(6):979-983.

Study #1 hypothesis being tested: Autism is linked to the disruption of the Galpha protein, which affects the hippocampal retinoid receptor pathways that are critical for vision, sensory perception, language processing and attention.

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<sup>65</sup> NICHD. *Facts About Autism*. Available at <http://www.nichd.nih.gov/publications/pubs/autism1.htm>

<sup>66</sup> Schettler T, Stein J, Reich F, et al. In harms way: Toxic threats to child development. Greater Boston Physicians for Social Responsibility 2000.

<sup>67</sup> Megson MN. Is autism a G-protein defect reversible with natural vitamin A? *Medical Hypotheses* 2000; 54(6): 979-983.

<sup>68</sup> London EA, Etzel RA. The environment as an etiologic factor in autism: a new direction for research. *Environmental Health Perspectives* 2000 Jun;108 Suppl 3:401-4.

<sup>69</sup> Schettler T, Stein J, Reich F, et al. In harms way: Toxic threats to child development. Greater Boston Physicians for Social Responsibility 2000.

<sup>70</sup> NICHD. *Facts About Autism*. Available at <http://www.nichd.nih.gov/publications/pubs/autism1.htm>

<sup>71</sup> Ibid.

<sup>72</sup> Ibid.

Study #1 findings: Study of 60 autistic children suggests that autism may be caused by insertion of a G-alpha protein defect into an already genetically predisposed child (e.g., child with at least one parent with a pre-existing G-alpha protein defect and has night blindness, pseudohypoparathyroidism or adenoma of the thyroid or pituitary gland.) The study found that treatment with natural vitamin A followed by blocked stimulation of acetylcholine receptors for neurotransmitters proved to be promising. Treatment resulted in improved vision, sensory perception, language processing, and increased attention. Recent evidence indicates that autism is a disorder of the nervous and immune system that affects multiple pathway and linked to the disruption of the G protein, affecting pathways of retinoid receptors in the brain.

Study #2: DeStefano F. Vaccines and Autism. Concise Reviews of Pediatric Infectious Diseases. 2001;20(9):887-888.

Study #2 hypothesis being tested: Measles-mumps-rubella (MMR) may be a causal agent of autism as well as other immunization factors such as pertussis immunizations, the thimerosal in vaccines, the receipt of multiple vaccine antigens, maternal peripartum rubella immunizations, and/or to genetic factors.

Study #2 findings: Studies published to date and epidemiologic data from Sweden, Great Britain, and California have not found an association between the MMR vaccine and the development of autism. The Immunization Review Committee of the Institute of Medicine as well as a special panel of the American Academy of Pediatrics both concluded that available evidence does not support this hypothesis. Published data are not available to determine whether autism may be related to other immunization factors such as pertussis immunization, thimerosal in vaccines, receipt of multiple vaccine antigens, maternal peripartum rubella immunizations, and/or to genetic factors.

Study #3: London EA, Etzel RA. The environment as an etiologic factor in autism: a new direction for research. Environmental Health Perspectives 2000;108(Suppl 3):401-4.

Study #3 hypothesis being tested: Environmental exposures during pregnancy could cause or contribute to autism based on their interaction with developmental genes in the fetus.

Study #3 findings: Evidence for environmental origin is circumstantial. The neurobiology of the prenatal developmental process and the environmental exposures that can effect those changes may serve as a clue. Retinoids are one promising area of research; as known modifiers of the Hox genes, retinoids may be a cause of autism because animal models involving retinoic acid have developed and share many of the brain lesions associated with autism including cerebellar malformations, cranial nerve and dopaminergic system abnormalities. Increased geographic clustering surveillance may also yield information linking environmental factors to autism. Though direct evidence for any etiology in autism is lacking, there are ample reasons for environmental research. Autism may be a disease of very early fetal development (approx. 20-24 days of gestation). Additional studies are needed to identify genetic abnormalities, basic neurobiology of the disease, and epidemiological studies.

**Hypothesis #21: Stress, neglect, and trauma caused by child abuse and maltreatment have adverse affects on a child's neurodevelopment.**

***General Information Related to Hypothesis #21***

- **Findings from the recent research (targeted search):** Information reported in the following five studies contributed to the above-mentioned hypothesis.

Study #1: Glaser D. Child abuse and neglect and the brain: A review. *Journal of Child Psychology and Psychiatry* 2000;41(1):97-116.

Study #1 hypothesis being tested: Child abuse and neglect are associated with adverse characteristics of neurodevelopment.

Study #1 findings: Studies demonstrate adverse effects on the brain from child abuse and neglect resulting in stress responses, including deregulation of the hypothalamic-pituitary adrenal axis and parasympathetic and catecholamine responses, and reduction in brain volume. There is evidence for changes in brain function in relation to child abuse and neglect. Child abuse/neglect and brain neglect could have implications on hyperarousal, aggressive responses, dissociative reactions, difficulties with executive functions, and education underachievement problems. Mechanism bringing about these changes need to be further studied, and may be more related to chronic abuse and neglect.

Study #2: Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry* 2001;49:1023-1039.

Study #2 hypothesis being tested: Persistent sensitization of the central nervous system as a consequence of early life stress may result in increased vulnerability to subsequent stress and development of depression and anxiety.

Study #2 Findings: Preclinical and clinical studies suggest that early life stress induces long-lived hyperactivity and sensitization of CNS, resulting in behavioral stress responsiveness. Findings from preclinical studies may be comparable to findings in adult patients with mood and anxiety disorders, however, more studies with human subjects exposed to early life stress are needed. There may be a genetic vulnerability to the neurobiological effects of early life stress.

Study #3: De Bellis MD. Developmental traumatology: a contributory mechanism for alcohol and substance use disorders. *Psychoneuroendocrinology* 2002;27:155-170.

Study #3 hypothesis being tested: Early childhood traumatic experiences are associated with an enhanced risk of adolescent and adult alcohol substance use disorder due to an

enhanced vulnerability for psychopathology, post-traumatic stress disorder (PTSD), and depression resulting from adverse influences on brain development.

Study #3 findings: Review of the literature suggests that childhood maltreatment and the diagnosis of PTSD are associated with an enhanced risk of adolescent and adult alcohol substance use disorders. The adverse influences of maltreatment on major biological stress response systems and brain development may contribute to the enhanced risk of adolescence and adult alcohol and substance abuse disorders. However, studies have relied on cross-sectional analyses of limited data and cannot definitively link the neurobiology of maltreatment-related PTSD with the neurobiology of alcohol and substance use disorders. Further research into the biological sequelae and mechanisms of symptom production in PTSD may help understand environmental-related mechanisms involved in the development of adolescent or young adult onset alcohol or substance use disorders.

Study #4: Bremner JD, Vermetten E. Stress and development: Behavioral and biological consequences. *Development and Psychopathology* 2001;13:473-489.

Study #4 hypothesis being tested: Early stress may have long-term effects on brain structures, affecting memory, learning, and lead to PTSD.

Study #4 findings: Animal models demonstrated that early stressors (during the last trimester of pregnancy) resulted in alternations in the morphological and behavioral development of the offspring and had long-term effects on neurobiology that persisted into adult life. However, the findings do not necessarily translate into human studies due to multiple complex factors such as copresence of neglect, family environment, variations in individual responses to stressors, and personalities. Early stressors to children result in long-term dysregulation of stress response systems and lead to changes in the brain. Studies indicate that childhood abuse has behavioral and biological consequences such as post-traumatic stress disorders. Understanding the effects of early stress on neurobiology provides a basis for studying the effects of childhood abuse on neurobiological development. Stressful environmental events can modify the way in which the genome is transcribed. Stress-induced changes in neurobiology underlie the development of psychopathology in those who do develop psychiatric symptoms. Depression is also an outcome of childhood abuse that affects neurobiological development.

Study #5: Wadhwa PD, Sandman CA, Garite TJ. The neurobiology of stress in human pregnancy: implications for prematurity and development of the fetal central nervous system. *Progress in Brain Research* 2001;133:131-142.

Study #5 hypothesis being tested: Prenatal psychosocial stress, social support, and personality variables may affect neuroendocrine parameters and alter fetal/infant brain development.

Study #5 findings: Results indicate significant associations between prenatal psychosocial factors and maternal neuroendocrine parameters. Psychosocial factors

were associated with increased hormone levels, and a combination of psychosocial and sociodemographic factors accounted for variance in measures of all neuroendocrine parameters in the study. Findings support the premise that maternal-placental-fetal neuroendocrine parameters are associated with features of maternal psychosocial functioning in pregnancy. Maternal psychosocial factors that affect the neuroendocrine system affect pregnancy outcomes and the fetal central nervous system.

**Hypothesis #22: Maternal immune response to infections can have an adverse effect on the fetus' neurodevelopment.**

***General Information Related to Hypothesis #22***

- **Findings from the recent research (targeted search):** Information reported in the following study contributed to the above-mentioned hypothesis.

Study #1: Patterson, PH. Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. *Current Opinion in Neurobiology* 2002;12:115-118.

Study #1 hypothesis being tested: Maternal immune response can influence fetal brain development through circulating cytokines.

Study #1 findings: Mouse models show that respiratory infection in the pregnant mother leads to significant changes in behavior and pharmacology of the offspring, some of which are applicable to schizophrenia and autism. Direct viral infection can have adverse health consequences for the developing fetus. Maternal infections lead to serious consequences for fetus (e.g., miscarriage, premature and still births, early neonatal deaths), and increase risk of mortality for the mother. Need to further study the link between maternal infection and mental illness. Also relevant for investigating potential therapies. More research about cytokines and corticosteroid levels is needed to better understand neuroimmune interactions.

**Hypothesis #23: In utero and postnatal exposure to methylmercury has adverse effects on a child's neurodevelopment and biobehavioral development.**

***General Information Related to Hypothesis #23***

- **Frequency/Load of exposure to mercury:**
  - According to the EPA, the highest emitters of mercury to the air include coal-burning power plants, municipal waste combustors, medical waste incinerators, and hazardous waste combustors. Emissions from these facilities gets deposited in water and land.
  - Human exposure to methylmercury primarily occurs through eating contaminated fish. Women of childbearing age who are exposed to methylmercury through consumption of contaminated fish are at a higher risk for health effects. As of July 2000, 40 states had issued fish consumption advisories due to contamination by mercury.<sup>73</sup>
- **Cost to individual/family/society/healthcare system :**
  - Differences in IQ have been associated with difference in educational achievement and average lifetime earnings.<sup>74</sup>
  - Though trivial on an individual level, when applied across populations, neurotoxins have a significant impact. A loss of 5 points in IQ is of minimal significance in a person with an average IQ. However, a shift of 5 IQ points in the average IQ of a population of 260 million increases the number of functionally disabled by over 50% (from 6 to 9.4 million).<sup>75</sup>
- **Findings from the recent research (targeted search):** Information reported in the following five studies contributed to the above-mentioned hypothesis.

Study #1: Sovikova E. Environmental risk factors in mental development of children. Toxicology Letters 2000;116:72.

Study #1 hypothesis being tested: Long-term exposure to lead and other metals causes deficits in cognitive functions of children.

Study #1 findings: Children living in areas with metallurgical plants performed worse on attention, memory, and intelligence tests than children in the control group. Additionally, the study found significant associations between lower cognitive ability level and unfavorable social and living environments (e.g., smoker in the family, lower income, lower family income, and nutritional problems, and lower education of mothers).

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<sup>73</sup> Environmental Protection Agency. *Mercury White Paper*. Available at: <http://www.epa.gov/ttn/oarpg/t3/memoranda/whtpaper.pdf>.

<sup>74</sup> Ibid.

<sup>75</sup> Ibid.

Study #2: Myers GJ, Davidson PW. Does methylmercury have a role in causing developmental disabilities in children? *Environmental Health Perspectives* 2000;108(3):413-420.

Study #2 hypothesis being tested: Exposure to methylmercury during pregnancy can have adverse effects on the offspring's development.

Study #2 findings: Study findings show that exposure to methylmercury in very high doses causes developmental disabilities. Exposure to high levels of methylmercury, a potent neurotoxin, can result in developmental disabilities that can cause mental retardation, cerebral palsy, and seizures. However, impact from low dose exposure from fish has been difficult to demonstrate because of differences in developmental/neurological testing, study populations, endpoints, designated covariates, and statistical methods used across the studies reviewed. More research is needed to determine: 1) a more accurate way to measure the magnitude, duration, and timing of exposure; 2) whether peak or mean mercury levels should be used to determine brain exposure; 3) biomarkers; 4) the differences between low and high dietary exposure differ; 5) and the importance of age at the time of exposure.

Study #3: Sandborgh-Englund G, Ask K, Belfrage E, Ekstrand J. Mercury exposure in utero and during infancy. *Journal of Toxicology and Environmental Health* 2001;63:317-320.

Study #3 hypothesis being tested: Based on measured blood levels, in utero exposure to mercury is greater than postnatal exposure to mercury.

Study #3 findings: Mercury levels in cord blood of newly born infants were two times higher than maternal blood mercury levels. At the end of the sampling period, mercury level in infants had decreased more than 45%, even though the infants had been consuming breast milk with mercury levels. Thus, exposure to mercury in utero is more significant than during infancy. Due to a very limited number of observations, a more full scale study is needed.

Study #4: Carpenter DO. Effects of metals on the nervous system of humans and animals. *International Journal of Occupational Medicine and Environmental Health* 2001;14(3):209-18. (Note: This study is also cited under the research area of *Biobehavioral Development*.)

Study #4 hypothesis being tested: Metals such as methylmercury and lead have negative effects on nerve cells and neurobehavioral functioning, leading to developmental problems or an increased risk of neurodegenerative disease in old age.

Study #4 findings: Studies show that lead exposure in young children results in loss of IQ, shortened attention spans, and anti-social behavior. Low doses of methylmercury have been found to have effects on cognition, while high doses impede brain development. High levels of aluminum exposure result in dementia. The findings are inconclusive as to whether exposure to metals result in neurodegenerative disorders

such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease.

Study #5: Carpenter DO. Effects of metals on the nervous system of humans and animals. International Journal of Occupational Medicine and Environmental Health 2001;14(3):209-18.

Study #5 hypothesis being tested: Metals such as methylmercury and lead have negative effects on nerve cells and neurobehavioral functioning, leading to developmental problems or an increased risk of neurodegenerative disease in old age.

Study #5 findings: Studies show that lead exposure in young children results in loss of IQ, shortened attention spans, and anti-social behavior. Low doses of methylmercury have been found to have effects on cognition, while high doses impede brain development. High levels of aluminum exposure result in dementia. The findings are inconclusive as to whether exposure to metals result in neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease.

**Hypothesis #24: In utero and postnatal exposure to lead has adverse effects on a child's neurodevelopment and biobehavioral development.**

***General Information Related to Hypothesis #24***

- **Frequency/load of exposure:**
  - One million children in the US exceed the currently accepted threshold for blood lead level exposure that affects behavior and cognition (10micrograms/dl). Updating the toxic threshold to be consistent with recent studies would further lower this threshold.<sup>76</sup>
  - Blood lead levels for children 6 and under have decreased by 75% between 1976 and 1991 due to elimination of leaded fuels and solder in food and drink cans.<sup>77</sup>
- **Special Populations:** Though lead levels have significantly fallen, many U.S. children from low income families in older, urban, housing remain exposed.<sup>78</sup>
- **Findings from the recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Sovikova E. Environmental risk factors in mental development of children. Toxicology Letters 2000;116:72.

Study #1 hypothesis being tested: Long-term exposure to lead and other metals causes deficits in cognitive functions of children.

Study #1 findings: Children living in areas with metallurgical plants performed worse on attention, memory, and intelligence tests than children in the control group. Additionally, the study found significant associations between lower cognitive ability level and unfavorable social and living environments (e.g., smoker in the family, lower income, lower family income, and nutritional problems, and lower education of mothers).

Study #2: Nevin R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environmental Research 2000;83(1):1-22. (Note: This study is also cited under the research area of Biobehavioral Development.)

Study #2 hypothesis being tested: Exposure to lead during the first three years of life causes adverse effects on cognitive abilities (measured by IQ tests), with positive correlations to such outcomes as unwed pregnancy and violent crimes.

Study #2 findings: Study findings support earlier research indicating that children with higher bone lead levels display more aggressive and delinquent behavior. Long-term trends in population exposure to gasoline and paint lead indicate that there is a strong association between exposure to lead and violent crimes and unwed pregnancy.

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<sup>76</sup> Ibid.

<sup>77</sup> Ibid.

<sup>78</sup> Wasserman GA, Liu X, Pine DS, Graziano JH. Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems. Neurotoxicology and Teratology 2001;23(1):13-21.

Study #3: Carpenter DO. Effects of metals on the nervous system of humans and animals. *International Journal of Occupational Medicine and Environmental Health* 2001;14(3):209-18. (Note: This study is also cited under the research area of *Biobehavioral Development*.)

Study #3 hypothesis being tested: Metals such as methylmercury and lead have negative effects on nerve cells and neurobehavioral functioning, leading to developmental problems or an increased risk of neurodegenerative disease in old age.

Study #3 findings: Studies show that lead exposure in young children results in loss of IQ, shortened attention spans, and anti-social behavior. Low doses of methylmercury have been found to have effects on cognition, while high doses impede brain development. High levels of aluminum exposure result in dementia. The findings are inconclusive as to whether exposure to metals result in neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease.

**Hypothesis #25:** Exposure to lead impairs fetal biobehavioral development by lowering IQ and increasing cognitive developmental dysfunction.

***General Information Related to Hypothesis #25***

- **Prevalence and incidence:** Young children have the greatest risk in the first 3 years when cognitive abilities are developing. Effects of lead exposure in IQ appear most evident and predictive around 10 years of age. (Fraction of an IQ point is lost per 1ug/dl increase of blood lead.<sup>79</sup>)
- **Cost to individual/family/society/healthcare system :**
  - Differences in IQ have been associated with difference in educational achievement and average lifetime earnings.<sup>80</sup>
  - Though trivial on an individual level, when applied across populations, neurotoxicants have a significant impact. A loss of 5 points in IQ is of minimal significance in a person with an average IQ. However, a shift of 5 IQ points in the average IQ of a population of 260 million increases the number of functionally disabled by over 50% (from 6 to 9.4 million).<sup>81</sup>
- **Frequency/load of exposure:** Blood lead levels for children 6 and under have decreased by 75% between 1976 and 1991 due to elimination of leaded fuels and solder in food and drink cans.<sup>82</sup>
- **Special Populations:** Though lead levels have significantly fallen, many U.S. children from low income families in older, urban, housing remain exposed.<sup>83</sup>
- **Findings from the recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Nevin R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. *Environmental Research* 2000;83(1):1-22.

Study #1 hypothesis being tested: Exposure to lead during the first three years of life causes adverse effects on cognitive abilities (measured by IQ tests), with positive correlations to such outcomes as unwed pregnancy and violent crimes.

Study #1 findings: Study findings support earlier research indicating that children with higher bone lead levels display more aggressive and delinquent behavior. Long-term trends in population exposure to gasoline and paint lead indicate that there is a strong association between exposure to lead and violent crimes and unwed pregnancy.

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<sup>79</sup> Nevin R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. *Environmental Research* 2000 May;83(1):1-22.

<sup>80</sup> Ibid.

<sup>81</sup> Ibid.

<sup>82</sup> Ibid.

<sup>83</sup> Wasserman GA, Liu X, Pine DS, Graziano JH. Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems. *Neurotoxicology and Teratology* 2001;23(1):13-21.

Study #2: Carpenter DO. Effects of metals on the nervous system of humans and animals. International Journal of Occupational Medicine and Environmental Health 2001;14(3):209-18.

Study #2 hypothesis being tested: Metals such as methylmercury and lead have negative effects on nerve cells and neurobehavioral functioning, leading to developmental problems or an increased risk of neurodegenerative disease in old age.

Study #2 findings: Studies show that lead exposure in young children results in loss of IQ, shortened attention spans, and anti-social behavior. Low doses of methylmercury have been found to have effects on cognition, while high doses impede brain development. High levels of aluminum exposure result in dementia. The findings are inconclusive as to whether exposure to metals result in neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease.

Study #3: Sovikova E. Environmental risk factors in mental development of children. Toxicology Letters 2000;116:72. (*Note: This study is also cited under the research area of Neurodevelopment.*)

Study #3 hypothesis being tested: Long-term exposure to lead and other metals causes deficits in cognitive functions of children.

Study #3 findings: Children living in areas with metallurgical plants performed worse on attention, memory, and intelligence tests than children in the control group. Additionally, the study found significant associations between lower cognitive ability level and unfavorable social and living environments (e.g., smoker in the family, lower income, nutritional problems, and lower education of mothers).

**Hypothesis #26:** Maternally related factors such as smoking, exposure to environmental tobacco smoke, and substance abuse during pregnancy negatively affect biobehavioral development.

***General Information Related to Hypothesis #26***

- **Frequency/load of exposure:** In some urban areas of the U.S., an estimated 10-45% of pregnant women consume cocaine. An estimated 1/1000 newborns in the U.S. are exposed in utero to opiates.
- **Findings from the recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Eskenazi B, Castorina R. Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children. *Environmental Health Perspectives* 1999 Dec;107(12):991-1000.

Study #1 hypothesis being tested: Environmental tobacco smoke (ETS) exposure to the fetus or child is associated with neurodevelopmental or behavioral effects. Specifically, there are adverse consequences to the child from maternal exposure to passive smoke during pregnancy or from the child's postnatal exposure to the smoke of others.

Study #1 findings: Active maternal smoking during pregnancy may be associated with negative effects on intellectual ability and behavioral problems. However, the impact of prenatal and postnatal ETS exposure is less clear. Animal and human data suggests that environmental tobacco smoke could cause subtle changes in child neurodevelopment and behavior. However, studies to date are difficult to interpret due to the influence of uncontrolled confounding factors, imprecision in measurements of smoking exposure, and co linearity of pre- and postnatal maternal smoking.

Study #2: Wasserman GA, Liu X, Pine DS, Graziano JH. Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems. *Neurotoxicology and Teratology* 2001;23(1):13-21.

Study #2 hypothesis being tested: There is an association between both maternal smoking during pregnancy and exposure to lead and behavioral development that is independent from social factors.

Study #2 findings: Adjusting for both social and average lifetime blood lead levels, prenatal smoking exposure proved to have significant increases in the total score on all testing subscales (e.g., aggressiveness, attention problems, thought problems) for children examined. Blood lead levels were shown to be significantly positively related to delinquency and to internalizing factors. Both maternal smoking and lead exposure are associated with childhood behavioral problems that continue into adulthood.

Study #3: Gressens P, Mesples B, Sahir N, Marret S, Sola A. Environmental factors and disturbances of brain development. *Seminars in Neonatology* 2001;6(2):185-94.

Study #3 hypothesis being tested: Fetal and neonatal brain development are influenced by environmental exposures to maternal and extra-maternal factors.

Study #3 findings: Studies demonstrate that exposure to ethanol, cocaine, anticonvulsants, viral infections, maternal diabetes, and untreated maternal phenylketonuria has a negative effect on brain development. It is highly likely that lead, heavy metals, benzodiazepines, and nicotine also have adverse effects on fetal brain development. There is a large variety of environmental factors and conditions that can interfere with fetal brain development, with maternal conditions representing a major source of factors. There is more need for controlled epidemiological studies addressing the impact of these factors and conditions. Also, there is a need to develop experimental models to better understand the real contribution and pathophysiological mechanisms of exposure effects on brain development.

**Hypothesis #27:** Broader societal factors such as neighborhood and community conditions can adversely impact a child's biobehavioral development.

***General Information Related to Hypothesis #27***

- **Findings from the recent research (targeted search):** Information reported in the following study contributed to the above-mentioned hypothesis.

Study #1: Caspi A, Taylor A, Moffitt TE. Neighborhood deprivation affects children's mental health: environmental risks identified in a genetic design. *Psychological Science* 2000;11(4):338-42.

Study #1 Hypothesis being tested: The neighborhoods in which children reside can exert a significant influence on the children's behavioral development beyond parental liability (e.g., selective migration) and heredity for behavioral or mental health problems.

Study #1 Findings: Study models indicated that children living in poor, neighborhoods ("neighborhood deprivation") have a small but significantly increased risk for behavioral problems, independent of any genetic predisposition toward mental or emotional problems. As such, neighborhood deprivation increases young children's behavioral and mental health problems. There is a need for additional studies to verify and document how these detrimental effects occur; study findings renew the impetus for community-level social intervention.

## **Targeted Research Area: Other—Childhood Obesity**

### **General Information on Childhood Obesity**

- **Prevalence and incidence of childhood obesity:** The prevalence of childhood obesity has more than doubled during the last two decades. Today, nearly 13% of children (ages 6-11) and 14% of adolescents (ages 12-19) are either overweight or obese. Hospitalizations for childhood obesity tripled to reach 1 percent of all hospitalizations of children.<sup>84</sup>
- **Mortality from childhood obesity:** This information was not readily available to Lewin.
- **Disease severity/disease burden:**
  - There has been a dramatic increase in chronic diseases associated with obesity in children, including type II diabetes and chronic disorders such as gall bladder disease and sleep apnea, as well as other disorders such as mental illness and asthma.<sup>85</sup>
  - From 1979 to 1999, childhood hospitalizations related to: diabetes nearly doubled from 1.43% to 2.36%, obesity tripled from 0.36% to 1.07%, gallbladder diseases tripled from 0.18% to 0.59%, and sleep apnea increase five-fold from 0.14% to 0.75%.<sup>86</sup>
- **Cost to individual/family/society/healthcare system:**
  - Health care costs from diseases related to childhood obesity increased from \$35 million (.43% of hospital costs) in 1979 to \$127 million (1.7% of hospital costs) in 1999 (based on 2001 constant US dollar value).<sup>87</sup>
  - Overweight children become overweight adults, who incur more than \$68 billion on health care related directly to obesity, representing 6% of US health care expenditures.<sup>88</sup>
- **Frequency/load of exposure:** This information was not readily available to Lewin.
- **Special Populations:**
  - Parental obesity doubles the likelihood of adult obesity among both obese and non-obese children under the age of 10.<sup>89</sup>
  - Poor white adolescents were 2.6 times more likely to be overweight than those in middle or high income families; overweight and obesity rates were highest for Mexican American males ages 6-11, African-American females ages 6-19, and adolescents ages 12-19 from low income households.<sup>90</sup>

*Hypothesis 28, described on the following pages, is associated with the Other Specialized Research Areas – Obesity targeted research area.*

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<sup>84</sup> Wang G, Dietz WH. Economic burden of obesity in youths aged 6 to 17 years: 1979-1999. *Pediatrics*. 2002 May;109(5):E81-1.

<sup>85</sup> Ibid.

<sup>86</sup> Ibid.

<sup>87</sup> Ibid.

<sup>88</sup> Center for Nutrition Policy and Promotion. *Facts about Childhood Obesity and Overweightness*. Family Economics and Nutrition Review. 1999; 12(1) 52-53.

<sup>89</sup> Ibid.

<sup>90</sup> Ibid.

**Hypothesis #28:** Altered intrauterine environment can affect fetal development leading to childhood obesity. Contributing factors include exposure to maternal diabetes, maternal malnutrition, and increased birth weight, which can alter fetal glucose tolerance and gene expression.

***General Information Related to Hypothesis #28***

- **Findings from the recent research (targeted search):** Information reported in the following two studies contributed to the above-mentioned hypothesis.

Study #1: Whitaker RC, Dietz WH. Role of the prenatal environment in the development of obesity. *Journal of Pediatrics* 1998;132(5):768-776.

Study #1 hypothesis being tested: Intrauterine environment altered by the mother influences risk of obesity in the child.

Study #1 findings: Increased birth weight and intrauterine exposure to maternal diabetes, particularly insulin dependent diabetes mellitus (IDDM), are both associated with higher weight in the child later in life. Although there is no evidence that obesity, per se, is programmed during gestation or that glucose intolerance alone causes obesity, the correlation between birth weight and the increased risk of obesity later in life suggest lasting effects of the intrauterine environment.

Study #2: Breier BH, Vickers MH, Ikenasio BA, Chan KY, Wong WPS. Fetal programming of appetite and obesity. *Molecular and Cellular Endocrinology* 2001; 185(1-2):73-79.

Study #2 hypothesis being tested: Environmental changes can reset or program the developmental path during intrauterine development leading to hyperphagia, obesity, cardiovascular and metabolic disorders later in life. The pathogenesis is not based on genetic defects, but on altered gene expression as a consequence of environmental adaptation of the fetus during fetal development. Varied nutrient availability at different stages of gestation, and both the timing and degree of reduced maternal nutrition may be important in determining precise postnatal phenotype.

Study #2 findings: Animal studies have shown that maternal malnutrition during pregnancy resulted in either increased levels of insulin receptors in adipocytes or enhanced insulin sensitivity of adipocytes in the offspring. These animal programming models demonstrate an association between a major rise in circulating insulin, leptin concentrations, and a large increase in appetite, and fat mass. Study findings provide in vivo evidence for altered endocrine communication between the hypothalamus, adipose tissue, and endocrine pancreas in pathogenesis of fetal programming-induced obesity.

## **Targeted Research Area: Other—Sudden Infant Death Syndrome (SIDS)**

### **General Information on SIDS**

- **Prevalence and incidence of SIDS:**
  - SIDS is the leading cause of death in infants between 1 month and 1 year of age. Most SIDS deaths occur when a baby is between 1 and 4 months of age.<sup>91</sup>
  - Between 1992 and 1997, the U.S. SIDS rate declined 38 percent from 1.2 deaths per 1,000 live births to 0.77 deaths per 1,000 live births.<sup>92</sup>
  - The decline in SIDS rate correlates with a decline in the proportion of infants who are placed to sleep on their stomachs and with an increase in the proportion of infants placed on their backs to sleep.<sup>93</sup>
  - The prevalence of infants placed prone to sleep declined at a steady rate between 1992 and 1997, from 70 percent to 21 percent. Since the initiation of the "Back to Sleep" campaign, there has been a substantial increase in infants being placed to sleep on their backs, from 27 percent in 1994 to 53 percent in 1997.<sup>94</sup>
- **Mortality from SIDS:** In 1999 there were 2,648 deaths from SIDS, accounting for 9.5% of all infant deaths; SIDS mortality rate is 66.9 deaths per 100,000 live births.
- **Disease severity/disease burden:** This information was not readily available to Lewin.
- **Cost to individual/family/society/healthcare system:** This information was not readily available to Lewin.
- **Frequency/load of exposure:** This information was not readily available to Lewin.
- **Special Populations:** Males are at greater risk for SIDS than females; African American infants are twice as likely to die of SIDS as white infants; American Indian infants are nearly three times more likely to die of SIDS as white infants; more SIDS deaths occur in colder months.<sup>95</sup>

*Hypothesis 29, described on the following pages, is associated with the Other Specialized Research Areas – SIDS targeted research area.*

<sup>91</sup> Center for Disease Control and Prevention. National Vaccine Program. Facts about SIDS. Available at [http://www.cdc.gov/od/nvpo/fs\\_tableVII\\_doc5.htm](http://www.cdc.gov/od/nvpo/fs_tableVII_doc5.htm).

<sup>92</sup> NICHD Pregnancy and Perinatology Branch. Report to the NACHHD Council. January 2000.

<sup>93</sup> Ibid.

<sup>94</sup> Ibid.

<sup>95</sup> <http://www.nichd.nih.gov/publications/pubs/sidsfact.htm>. Prepared by NICHD Public Information and Communications Branch April 1997

**Hypothesis #29:** Infectious bacterial agents such as *Helicobacter pylori*, *Staphylococcus aureus*, and *Escherichia coli* and their toxins may be causal factors for SIDS.

***General Information Related to Hypothesis #29***

- **Findings from the recent research (targeted search):** Information reported in the following study contributed to the above-mentioned hypothesis.

Study #1: Blackwell CC, Weir DM. The role of infection in sudden infant death syndrome. *FEMS Immunology and Medical Microbiology* 1999;25:1-6.

Study #1 hypothesis being tested: Infection from the toxins of invasive bacterial agents such as *Helicobacter pylori*, *Staphylococcus aureus*, *Escherichia coli*, *Bordetella pertussis*, and *Haemophilus influenza* may cause SIDS.

Study #1 findings: Study findings are inconclusive. Data showed no direct evidence as to how inflammatory mediators, in response to the bacterial toxins, could cause fatal alterations in the physiology of the infant. However, an infectious etiology fits the known risk factors of SIDS: specific age range affected, nocturnal deaths, exposure to cigarette smoke, overheating, high incidence in lower socioeconomic groups and in some ethnic groups in which serious respiratory infections are major causes of infant deaths. As such, SIDS deaths may be due to patho-physiological responses elicited by microbial products and/or cigarette smoking that impede an infant's endocrine system's ability to combat inflammatory mediators.