CHILD NEURODEVELOPMENT FOLLOWING IN UTERO EXPOSURE TO ORGANIC SOLVENTS

by

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Abstract

BACKGROUND: Many women of reproductive age are employed in industries involving exposure to organic solvents. Animal toxicological studies and human case reports demonstrate that exposure to organic solvents can cause neuropsychological deficits in exposed offspring; however, there is limited data from prospective controlled human studies.

OBJECTIVE: To compare neuropsychological functioning between children whose mothers were occupationally exposed to organic solvents during pregnancy with a non-exposed matched comparison group.

METHODS: Participants were 48 women who had previously contacted the Motherisk Program in Toronto, Canada during pregnancy regarding occupational exposure to organic solvents and a matched comparison group of women with no known exposure to teratogens during pregnancy. Children (18 months to 8 years 11 months at time of study) were compared in areas of cognitive, language, motor, and behavioral functioning.

RESULTS: Children whose mothers were exposed to organic solvents during pregnancy displayed a lower level of functioning when compared with their matched peers in areas of cognitive, language, motor, and behavioral domains. Although the scores on measures of
behavioral functioning were not in the clinical range, the mothers of exposed children reported more challenging behavioral problems.

In order to determine whether exposure predicted neuropsychological outcomes above and beyond maternal intellectual functioning, hierarchical regressions were run with maternal IQ and maternal education at Step 1 and exposure status added at Step 2. In utero exposure to organic solvents predicted lower scores on global measures of Verbal IQ, receptive and expressive language scales above and beyond maternal intellectual functioning. Factors associated with higher levels of exposure (detecting odor, longer duration and total number of toxicity symptoms) was associated with poorer outcome on behavioral and motor functioning tests.

CONCLUSION: Despite the fact that the exposed mothers experienced minimal symptoms of toxicity, detrimental effects were still evident in their offspring. Current safety standards for exposure were designed for adults and need to be reevaluated. Further studies addressing exposure to specific organic solvents, dose, and gestational timing of exposure are warranted.
Acknowledgments

This thesis is the culmination of a journey that started while working with Dr. Gideon Koren and other wonderful people at Motherisk. The Motherisk Program at the Hospital for Sick Children is one of the most stimulating and exciting places to learn. I want to thank Dr. Koren for initially recommending this interesting and important topic of research. He is a creative and inspirational man who motivates many through wonderful journeys into the intriguing area of maternal-fetal toxicology. Dr. Koren has created an environment at Motherisk that is unlike any other, students, Fellows and staff are always smiling and laughing, creating an environment that can only foster enthusiasm and extraordinary productivity. I thank Dr. Koren for building such an amazing place for so many to flourish and for being an exceptional mentor.

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I dedicate this thesis to my family who are all a source of inspiration and enduring motivation. My parents have, from the moment I can remember, encouraged me to fulfill my greatest dreams and reach for the highest goals imaginable. I am eternally thankful for your love and support. You can now take the opportunity to enjoy your life to the fullest possible. I also want to thank Sharon Atnikov for her constant and generous support. I can’t imagine a more wonderful mother-in-law and friend than Sharon. I feel very fortunate to have you in my life.

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Chapter 1

Overview and Introduction
1.1 Overview and Introduction

Over the past several decades there has been a burgeoning of research aimed at identifying agents that may be harmful to both the physical and neurological development of the unborn child. Teratogens are chemical or physical agents that cause abnormalities of either a structural or functional nature following exposure during pregnancy. Teratogens have the capability of crossing the placenta and present a direct hazard to the developing fetus. The effect of a teratogenic exposure is related to the specific agent, dose, duration, and timing of exposure during fetal development. The effects can be evidenced as anatomic malformations as well as functional, metabolic, neuropsychological, or behavioral abnormalities. Fetal exposure to potential teratogens may occur via maternal inhalation, oral ingestion or dermal touch (Dick, 2006).

Women represent a significant portion of the workforce in most developed countries. It is estimated that 17% of women who work during their pregnancy are exposed to known teratogens in their occupational environment (Bentur & Koren, 1991), whereby repeated exposure to various chemicals throughout pregnancy may occur. Statistics Canada reported that 8.1 million women were employed outside the home in Canada in 2009, representing 47% of the workforce (Ferrao & Williams, 2011). The U.S. Department of Labor reported that 72 million women were employed in the United States in 2010 (Cook & Lott, 2011). In the European Union, 40% of the workforce in 2003 was female (2002). Seventy five percent of all working women are of child-bearing age and 63% of these women were employed during their pregnancy in North America (Sharara et al., 1998, Bowen & Hannigan, 2006).

Approximately 10 million Americans are exposed to organic solvents on a daily basis in their occupational setting (NIOSH, 1987), making organic solvents one of the most prevalent types of chemical exposure. Organic solvents are also one of the most prevalent sources of workplace chemical exposure reported by pregnant women (Bentur & Koren, 1991,
McDiarmid & Gehle, 2006, NIOSH, 1987), thus it is essential to investigate their safety during pregnancy. The vulnerability of the developing fetus to environmental toxicants makes it essential for clinicians / physicians to consider the workplace environment of their patients during pregnancy to ensure the safety of the developing fetus (Perrin et al., 2007).

Animal toxicology studies, human case reports as well as a small number of empirical investigations have demonstrated the physical and neurological consequences of exposure to organic solvents in adults and the fetus (Arai et al., 1997, Arnold et al., 1994, Bordarier et al., 1991, Bowen et al., 2005, Bowen & Hannigan, 2006, Bowen et al., 2007, Burry et al., 2003, Costa et al., 2002, Costa & Manzo, 1998). However, the studies specifically looking at neuropsychological consequences associated with in utero exposure to organic solvents are few and have been limited in their study design and sample size. The following is a review of the literature on organic solvents, occupational settings where exposure may occur, as well as the effects of exposure to organic solvents in: animals, adults, children, and the fetus.

1.2 Organic Solvents

Organic solvents are carbon-based solvents (they contain carbon in their molecular structure) that are commonly employed to extract, dissolve or disperse substances without causing a chemical change to either the compound or the solvent itself (Garlantezec et al., 2009). Organic solvents are in a liquid state at temperature between 0º - 250ºC (NIOSH, 1987) and are found in industrial settings, the home environment (cleaning products), contaminated drinking water, or in the air from nearby industry. Exposure to organic solvents in the home environment is more likely to be of short duration, while exposure in the occupational setting is often of a more chronic nature (Logman et al., 2005). Despite the fact that organic solvents have been in use for over 100 years, there was little information in the medical literature regarding their neurotoxic effects until the 1940s and no significant research conducted until the late 1960s (Hartman, 1995). The National Institute for Occupational Safety and Health
(NIOSH) now certifies many organic solvents as carcinogens (e.g., benzene, carbon tetrachloride, trichloroethylene), reproductive hazards (e.g., 2-ethoxyethanol, toluene), and neurotoxins (e.g., n-hexane, tetrachloroethylene, toluene) (Garlantezec et al., 2009).

### 1.3 Organic Solvents: Associated Risk of Toxicity

#### 1.3.1 Organic Solvents in Occupational Environments

Organic solvents are used in a plethora of industries including: biotechnology (in enzymatic reactions) (Matsumoto et al., 2001); aerospace manufacturing (metal finishing process); asphalt compounding (Wypych, 2001); cosmetic and personal care products such as nail polish and nail polish remover (solvents such as acetone, methyl acetate, ethyl acetate, methyl butyl acetate, methyl glycol, toluene, xylene, methyl chloroform, and naptha often constitute approximately 70% of nail polishes), fragrances, hair dyes, cleansers, hair sprays and setting lotions (Wypych, 2001); dry cleaning and treatment of textiles such as waterproofing (tetrachloroethylene-TCE/ perchloroethylene-PCE) (Hasenclever, 2001); electronic industry cleaning products (printers, communication devices, automotive, as well as air and spacecraft) (Hanek et al., 2001); food industry to extract oils (Wakelyn & Wan, 2001); wood preservation (Hahn et al., 2001); medical application such as the development of medical devices using polyurethanes which are processed using solvents (Wypych, 2001); paints and coatings (Hahn et al., 2001); petroleum refining (Wypych, 2001); pharmaceuticals in the manufacturing of drug substances and products (Bauer & Barthelemy, 2001); printing (inks, adhesives, print machinery cleaners) (Wypych, 2001); shipbuilding and repair (Serageldin & Reeves, 2001); manufacturing of glass, clay and pottery products, and plaster (Wypych, 2001); as well as wood furniture including the use of adhesives, veneers, pretreatment, finishing products such as stains, paints, fillers, and inks (Wypych, 2001). The neurotoxicity of \( n \)-hexane is the most commonly studied solvent, it is an aliphatic
hydrocarbon in liquid form (Kumar, 2008). Table 1 delineates organic solvents into specific types of solvents as well as the industries or environments in which exposure may occur.
**Table 1**

*Organic Solvents and Industries of Exposure*

<table>
<thead>
<tr>
<th>Class of organic solvent</th>
<th>Example of solvent</th>
<th>Industry of exposure / use of organic solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliphatic hydrocarbon</td>
<td>n-hexane, mineral spirits, varnish, kerosene</td>
<td>Furniture / wood manufacturing and refinishing, glue for shoe manufacturing, automobile construction, textile manufacturing, cleaning and degreasing machinery, spot removers</td>
</tr>
<tr>
<td>Aromatic hydrocarbons</td>
<td>Benzene / toluene</td>
<td>Precursor in production of drugs, plastics, used in synthetic rubber, dyes, to dissolve paints, thinners, printing ink, disinfectant, octane booster in gasoline fuels, used to break open red blood cells to extract hemoglobin in biochemical studies</td>
</tr>
<tr>
<td>Halogenated hydrocarbon</td>
<td>Carbon tetrachloride / trichloroethylene / tetrachloroethylene (perchloroethylene)</td>
<td>Banned in consumer products in 1970’s, previously used in dry cleaning, as a refrigerant, in fire extinguisher and pesticides, synthetic chemistry research, food industry, degreaser for metal parts</td>
</tr>
<tr>
<td>Alcohols</td>
<td>methanol</td>
<td>Used as an antifreeze, in engines of automobiles, as a gasoline additive</td>
</tr>
<tr>
<td>Cyclic hydrocarbons</td>
<td>Cyclohexane</td>
<td>Used in the production of nylon and in chemical laboratories</td>
</tr>
<tr>
<td>Esters</td>
<td>Ethyl acetate</td>
<td>Glue, nail polish and removers, decaffeinates coffee beans and tea, in perfumes, used in wines, entomology to kill insect without destroying body</td>
</tr>
<tr>
<td>Class of organic solvent</td>
<td>Example of solvent</td>
<td>Industry of exposure / use of organic solvent</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Ethers</td>
<td>Ethyl ether</td>
<td>Used in laboratories, previously used as an anesthetic</td>
</tr>
<tr>
<td>Nitrohydrocarbons</td>
<td>Ethyl nitrate</td>
<td>Ingredient in drugs, dyes, and perfume</td>
</tr>
<tr>
<td>Ketones</td>
<td>Acetone / methylethylketone</td>
<td>Nail polish and glue remover, used to make plastic, drugs, fibers, degreaser, clean glass and porcelain, used in laboratory settings, and as a fuel additive</td>
</tr>
<tr>
<td>Glycols</td>
<td>Ethylene glycol</td>
<td>Antifreeze, used in plastics industry, laboratory setting</td>
</tr>
<tr>
<td>Aldehydes</td>
<td>Acetaldehyde</td>
<td>Chemical laboratories</td>
</tr>
</tbody>
</table>


Occupations with the highest intensity of exposure include: dry cleaning, printing, industrial painting, manufacturing of glass, manufacturing of reinforced plastic, and tile fixing. Moderate exposure industries include: house painting, mechanics, assembly processes using solvents, paint making, and industrial degreasing. Industries where low intensity of exposure occur include: gasoline fuel attendant, carpentry, chemical process operator, laboratory technician, and nail technician (Dick, 2006, Nunes de Paiva & Pereira Bastos de Siqueira, 2005). The most prevalent female-dominated occupations with potential organic solvent exposure include health care workers, the clothing and textile industries (Tikkanen & Heinonen, 1988, Hemminki, 1980), as well as beauty salons and scientific laboratories (Kersemaekers et al., 1998, Gjolstad et al., 2006, LoSasso et al., 2002, van Muiswinkel et al., 1997).
Toluene and mixtures of solvents containing toluene and ethers, ketones and hexanes represent the most common type of organic solvent exposure (Nunes de Paiva & Pereira Bastos de Siqueira, 2005). Although each specific type of organic solvent is heterogeneous, the compounds are typically referred to as a group as they tend to possess common characteristics including their volatility, odor, vapor pressure capacity, solvency, and capacity of travelling through layers of the skin (Hartman, 1995, Curtis et al., 1986). The occupational health literature suggests that exposure to organic solvents in humans is most often characterized by exposure to a mixture of multiple solvents rather than one specific solvent (Kramer et al., 1999, Angerer & Kramer, 1997, NIOSH, 1987) and the particular purpose for the solvents dictates the composition of the mixture. Incidental exposure to vapors from gasoline, lighter fluid, spot and paint removers may be of short duration and at low levels, and hence may go undetected (Eskenazi et al., 1988). More serious exposure to paint removers as well as floor and tile cleaners may occur where large quantities of solvents are used in manufacturing and processing operations.

The central nervous system consists of a large amount of lipids and has an extensive vascular supply. Since organic solvents are fat soluble, they tend to accumulate in the central nervous system in high concentration (Johnson et al., 1987). There are substantial data regarding the neurotoxic effects in adults following exposure to organic solvents in occupational settings (Bockelmann et al., 2004, Jovanovi et al., 2004, Nilson et al., 2002, Vital et al., 2006). The neurological impairment may be evident both neuroanatomically and functionally. The neuroanatomic findings have linked exposure with axonal degeneration and lesions of the myelin sheath, asymmetric central and cortical atrophy, focal abnormalities in the parieto-occipital areas, cerebral blood flow abnormalities (Amaral et al., 1994, Juntunen et al., 1980, Vital et al., 2006), supranuclear palsy (McCrank & Rabheru, 1989), and disturbance of striatal dopaminergic function (Edling et al., 1997).

Organic solvent exposure in adult humans is often characterized by a cluster of neurotoxic symptomatology (Costa & Manzo, 1998). Adults who have been acutely exposed to organic
solvents may report symptoms of fatigue, difficulty concentrating, dizziness, depressed mood, and drunken feeling, whereas those chronically exposed may suffer irreversible central nervous system damage (Johnson et al., 1987, Vital et al., 2006). Exposure to organic solvents may result in cerebellar dysfunction, encephalopathy, optic and/or cranial neuropathy, neurodegenerative diseases such as Parkinson’s disease, Alzheimer’s disease, essential tremor, multiple sclerosis, motor neuron disease or amyotrophic lateral sclerosis, peripheral neuropathy, as well as impairments in senses including taste, olfaction, auditory function, and vision (Zibrowski & Robertson, 2006, Till et al., 2005, Dick, Filley & Kelly, 2001, Rosenberg, 1995, Sharp & Rosenberg, 1997, Hageman et al., 1999, van der Hoek et al., 2000, van der Hoek et al., 2001, Triebig & Hallermann, 2001, Yu et al., 2004).

The neurotoxic functional effects have been associated with cognitive deficits including speed of information processing, memory, attention, verbal fluency, psychomotor impairment (Baker, 1988, Daniell et al., 1999, Spurgeon et al., 1992, Triebig et al., 1992, Wood & Liossi, 2005); psychiatric disturbances such as personality changes (Juntunen et al., 1980), depression (Evans & Balster, 1991, Daniell et al., 1999, Fernicola et al., 1991, Morrow et al., 2000, Morrow et al., 2001), and a feeling of narcosis; as well as physiological effects including anesthesia, respiratory arrest, unconsciousness, or death (Garlantezec et al., 2009).

1.3.2 Mechanism of Solvent Toxicity and Species Specificity

A wide range of organic solvents share chemical properties of relatively high volatility and high vapor pressure that contribute to inhalation exposure risk. Inhalation absorption through the lungs is dependent on the concentration of the inhaled solvent, its solubility, as well as the pulmonary ventilation rate (Baker et al., 1985, Baker, 1988). Exposure is mediated by the type of ventilation and use of protective equipment and gear worn (Baker et al., 1985). The extent of absorption in the skin is dependent on duration of exposure, organic solvent concentration, state of the skin, and solubility of the organic solvent. Exposure may also
occur through other routes such as contaminated underground water (Schardein, 2000, Matsumoto et al., 2001). During pregnancy, when the mother has an increased respiration rate and oxygen consumption, organic solvents can interfere with oxygen uptake and can adversely affect the circulation of red blood cells (Red et al., 2011, Strassner & Chyu, 1992).

Schardein (2000) noted that in animal studies the specific route of exposure may result in different teratogenic effects and malformations may also differ between species. For example, exposure to acetonitrile through inhalation resulted in brain and rib malformations in hamster embryos (Willhite, 1981, Willhite et al., 1981); oral or inhalation exposure to acetonitrile in rat embryos resulted in increased mortality but no malformations (Saillenfait et al., 1993); and oral administration of acetonitrile in rabbits was not teratogenic, even at levels that were toxic to the mother (Mast et al., 1986). This selective developmental toxicity can be particularly concerning in humans when toxic effects are detectable in the fetus but undetectable in the mother as she is not experiencing any of the symptoms commonly associated with organic solvent toxicity (Schardein, 2000).

The etiology of many malformations or neuropsychological deficits is often multifactorial and may result from teratogenic exposure, genetic factors, or a combination of the two. Of critical importance is the timing of exposure, specifically during the sensitive period when morphogenesis (differentiation of cells and tissues that form the various organs and parts of the body) is taking place. Sensitive periods of pregnancy are very specific stages of active embryonic differentiation and morphogenesis. A known teratogen may have no effect on embryonic development if exposure occurs prior to or following the critical sensitive period when a specific structure is susceptible to that particular teratogen (Larsen, 2001). For example, if two embryos are at slightly different stages of development and are exposed to the same dose of the same teratogen, one may develop a malformation while the other may be unaffected (Larsen, 2001). The human fetus is considered to be most vulnerable to structural abnormalities during the period of organogenesis, which takes place during the first trimester of pregnancy. However, the central nervous system in humans develops throughout
pregnancy and well into the second year of life, leaving it vulnerable to external insult throughout pregnancy, breast feeding and into childhood.

Dose-response levels are often based on safe exposure limits in adults such as the “8-hour Time Weighted Average” limit (TWA), which is the concentration of a substance in air which may not be exceeded over an eight hour work period (WorkSafe, 2003) or the ‘reference dose’ (RfD) or ‘reference concentration’ (RfC) which is an estimate of the dose or concentration in humans that is unlikely to result in adverse health problems (Polifka & Faustman, 2002). Extrapolating safe limits for pregnant women based on these values could be dangerous as a dose-response level has not been established for human pregnancy. Moreover, as noted above, exposure to levels considered the RfD may produce no symptoms of toxicity in the mother, but may results in teratogenic consequences to her fetus.

1.3.3 Genetic Susceptibility

In recent years techniques have been developed to study chromosomal and DNA changes associated with organic solvent exposure. These changes can be used as biological markers, which are important clinically to determine levels of toxicity and aid in establishing etiology. Susceptibility markers, which are genetic factors that increase an individual’s sensitivity to environmental toxins, were discussed at the 6th International Symposium on Biological Monitoring in Occupational and Environmental Health in 2005 as one of the important markers coming to the forefront of change in regulatory bodies within Europe (Scheepers & Heussen, 2005). Biological monitoring of exposure enables researchers and clinicians to specify the type and quantity of solvent exposure (Schardein, 2000). Biological monitoring enables measurement of the internal dose of exposure within the human body and the type of chemical exposure (i.e., toluene versus benzene exposure). The markers correspond to the unchanged organic solvent evidenced in blood analysis, metabolites of the organic solvent excreted in urine, serum bile acids, measurement of unchanged organic solvent in alveolar air, or mass spectrometry (Kramer et al., 1999, Angerer & Kramer, 1997, Nadeau et al.,
Mass spectrometry is an instrument that has the capability of identifying or weighing chemicals in a substance by its mass and charge.

Lawson et al. (2006, 2003) defined two categories for grouping individuals according to their vulnerability to environmental toxins: those who possess a particular allele that place them at elevated risk for disease or birth defects irrespective of other influences such as environmental exposures, and those with what is termed susceptibility genes, which increase the risk of disease or birth defects and are dependent on the interaction of genetics and environmental exposures. This interaction between environmental teratogens and susceptibility genes may play a role in determining the manifestation of a birth defect or neurologic consequence in the fetus versus no effect (Lawson et al., 2003). For example, low-level occupational exposure to benzene has been associated with two susceptibility genes that result in decreased length of gestation, suggesting a gene-environment interaction (Wang et al., 2000). Specific maternal and infant genotypes can modify the effect of organic solvent exposure on gestational age, either causing a shortened gestational period for specific genotypes or no effect on gestational age with the same organic solvent exposure in those with different genotypes. This genotype specific interaction with organic solvent exposure was evidenced even at low levels of exposure (Qin et al., 2008).

The mechanism of solvent toxicity at the chromosomal level is known for only a few specific compounds. For example, Karaci and colleagues (1995) suggested that low level exposure to benzene may be related to genotoxicity. McGregor (1994) indicated that exposure to toluene has also been associated with genetic aberrations. The toxicity of toluene is suspected to be related to its lipid dissolving capabilities and/or its inhibition of protein synthesis.
1.3.4 Animal Neurotoxicity Associated With In Utero Exposure to Organic Solvents

Numerous animal studies have found a direct correlation between in utero exposure to organic solvents and symptoms of neurotoxicity in the offspring (Daniel & Evans, 1982, Nelson et al., 1984, Stoltenburg-Didinger et al., 1990, Zhu et al., 2006). Zhu and colleagues (2006) and Gospe & Zhou (1998) reported that high dose exposure to organic solvents, such as toluene, in pregnant rodents resulted in impaired neurobehavioral development in offspring. The functional abnormalities include abnormal cortical and hippocampal EEG activity (Tomas et al., 1999), changes in acetylcholine metabolism (Honma, 1983), enzyme inhibition disturbing the homeostatic regulatory functions of astrocytes (Vaalavirta & Tahti, 1995), CNS depression (Evans & Balster, 1991), CNS malformations (Schardein, 2000) including cochlear injury (Liu & Fechter, 1997), hydrocephalus and exencephaly (Kato, 1958), as well as cortical abnormalities (Gospe & Zhou, 2000).

1.3.5 Research on Childhood Exposure to Organic Solvents

Occupational exposure to organic solvents in children is also associated with neurotoxic consequences (Saddik et al., 2003, Saddik et al., 2005). Saddik et al. (2005) studied 300 children in Lebanon who were between the ages 10 through 17 years. These children were divided into three groups: 100 children exposed to organic solvents at work, 100 children who were working but not exposed to organic solvents in their occupational environment, and 100 children who did not work. The groups were compared using the Q16 Neurotoxic Questionnaire (1984) for symptoms specifically related to central nervous system (CNS) effects of organic solvent exposure as well as a battery of neurobehavioral tests including: the Profile of Mood States to assess symptoms of anxiety and depression (Pollock et al., 1979); the Grooved Pegboard Test as a measure of manual dexterity (Trites, 1989), the Digit Span sub-scale from the Wechsler Intelligence Scale for Children-Revised, which assesses attention, concentration and working memory (WISC-R) (Wechsler, 1991); and the Draw a
Person test as an estimate of intellectual functioning (Naglieri, 1988). The results indicated that children scored significantly higher than the two non-exposed groups on the Q16 Neurotoxic Questionnaire. The exposed children performed more poorly on: the WISC-R digit span forward, which is a measure of attention, concentration and working memory; the Grooved Pegboard Test dominant and non-dominant hand, which assesses manual dexterity; as well as the Profile of Mood States when compared with the non-exposed groups. The authors suggested that, similar to adult organic solvent exposure, the exposed children showed deficits in reaction speed and memory functioning.

Increased awareness and education about the potential for chemical exposure toxicity coupled with labour standard laws over most developed countries have resulted in fewer childhood occupational organic solvent exposures. Thus, the studies by Saddik and his group represent the only empirical data assessing the neuropsychological consequences of childhood occupational organic solvent exposure. This information is important as it confirms neurotoxic effects associated with exposure not only in adulthood but also in childhood (Muttray et al., 2005, Baker et al., 1985, van Hout et al., 2006). This could support the hypothesis that the fetal brain might be vulnerable despite the plasticity of the young developing brain.

### 1.3.6 Teratogenicity Associated With In Utero Exposure to Organic Solvents

The following are examples of malformations exhibited following exposure to organic solvents: CNS defects (McMartin et al., 1998) such as neural tube defects (NTDs) (Holmberg, 1979, Kurppa et al., 1983, Holmberg & Nurminen, 1980, Khattak et al., 1999), oral clefts (Chevrier et al., 2006, Holmberg, 1979, Holmberg et al., 1982, Khattak et al., 1999), cardiovascular malformations (Loffredo, 2000, Tikkanen & Heinonen, 1988), fetal solvent/gasoline syndrome (FSS) (Arnold et al., 1994, Bowen et al., 2005, Bowen et al., 2007, Costa et al., 2002, Hersh, 1989, Pearson et al., 1994, Toutant & Lippmann, 1979),
esophageal stenosis (Meirik et al., 1979), omphalocele and gastroschisis (Aarva & Svele, 1986, Erickson et al., 1978, Torfs et al., 1996), sacral agenesis (Kucera, 1968), and renal-urinary tract defects (McDonald et al., 1987, Garlantezec et al., 2009).

In a meta-analysis conducted by McMartin et al. (McMartin et al., 1998) occupational exposure to organic solvents increased the risk for major malformations. The meta-analysis included 5 retrospective studies (Axelsson et al., 1984, Cordier et al., 1992, Holmberg et al., 1986, Lemasters, 1983, Tikkanen & Heinonen, 1988), the majority of which were based on case reports. Many studies did not control for potential confounding variables such as maternal age and IQ, smoking, alcohol use, or concurrent drug use (McMartin et al., 1998). Khattak et al. (1999) reported that women who were occupationally exposed to organic solvents had a 13-fold increased risk for having offspring with major malformations. A significant proportion of the malformations found occurred in women who complained of symptoms of toxicity (i.e., eye and respiratory tract irritation) (Khattak et al., 1999).

A retrospective Finnish study (Holmberg & Nurminen, 1980) reported that mothers of infants with central nervous system malformations were four times more likely to have been exposed to one of 14 different organic solvents during their pregnancy than mothers of infants without such defects. In most of these cases the women were exposed to levels of organic solvents below the recommended occupational thresholds in Finland (Holmberg & Nurminen, 1980). In a study examining congenital anomalies in a retrospective cohort of mothers who were exposed to tetrachloroethylene-contaminated drinking water during their pregnancy, the authors reported an increased risk for a number of different congenital anomalies (Aschengrau et al., 2009). Several studies have also suggested that maternal occupational exposure to organic solvents is associated with an increased risk for malformations in their offspring including anencephaly and deformations of the musculoskeletal system (Aguilar-Garduno et al., 2010).
Till and colleagues (2005) reported that maternal exposure to organic solvents was associated with vision abnormalities including reductions in contrast sensitivity, grating acuity as well as an increased risk of color vision impairment in offspring.

### 1.3.7 Pregnancy Outcome

In addition to malformations, other adverse pregnancy outcomes have also been linked to organic solvent exposure during pregnancy (Stillerman et al., 2008). For example, there is a reported increased risk for spontaneous abortion (Bukowski, 2001, Agnesi et al., 2003, Jones & Balster, 1998, Khattak et al., 1999, Lindbohm et al., 2007, Lindbohm et al., 1990, Windham et al., 1991), neonatal complications (Mukhametova & Vozovaia, 1972), decreased birth weight, infants large for gestational age, as well as small-for-gestational age (Ahmed & Jaakkola, 2007), and impaired fertility (Agnesi et al., 1997, Axelsson et al., 1984, Kumar, 2004, Sallmen et al., 2006, Wennborg et al., 2001, Windham et al., 1991, Sallmen et al., 2008). Khattak et al. (1999) noted that exposure to organic solvents throughout pregnancy was associated with significantly lower birth weight and more fetal distress than exposure for less than 7 months of pregnancy, suggesting that there may be a dose-response and timing effect of exposure.

### 1.4 Organic Solvent Abuse

#### 1.4.1 Cognitive, Behavioral and Psychiatric Effects of In Utero Exposure to Organic Solvents

The literature reviewed above suggests that exposure to organic solvents may be associated with a myriad of potential teratogenic effects both in the animal and human literature. However, there is a paucity of data on the effects that exposure to organic solvents during
pregnancy might have on the neuropsychological functioning in offspring. Although neuropsychological and behavioral consequences of in utero exposure might not be physically evident in the child at birth, the lifelong challenges that these consequences may pose can be significant.

Eskenazi, et al. (1988) conducted a study on neuropsychological and behavioral functioning in children between the ages of 3 and 4 years whose mothers were exposed to one of several types of organic solvents at some time during pregnancy. The neurocognitive assessment battery included the McCarthy Scales of Children’s Abilities (McCarthy, 1972), the Conners Parent Scale of Hyperactivity (Goyette et al., 1978), the National Institute of Mental Health Childhood Personality Scale-Revised (Dibble & Cohen, 1974). The results indicated that, compared to a matched unexposed group, there were no significant neuropsychological or behavioral problems in the exposed children. The only significant difference reported was that those children whose mothers were exposed throughout pregnancy began to walk later than those who were not exposed throughout pregnancy.

Eskenazi et al. (Eskenazi et al., 1988) noted that a limitation in their study was the short age span of the children, suggesting that earlier effects might have been compensated for by brain plasticity by 3 years of or latent effects may not yet be apparent by 4 years of age. The investigators selected 98 occupations in which organic solvent exposure may have occurred. The mothers were selected from a cohort of women who had given birth between 1980 and 1982. The exposed group of women included in the study were exposed to an organic solvent at an unspecified time during pregnancy, thus it is unknown if the fetus was exposed during the first trimester of pregnancy while the important phase of organogenesis was taking place. The outcome measures may not have been sensitive enough to detect differences between the two groups (Eskenazi et al., 1988). The authors suggested that a more extensive neuropsychological assessment battery that included language assessment might yield different results. The investigators also determined, on analysis of results, that some women who reported being exposed to organic solvents may in fact not have been exposed at all,
suggesting that there may have been response bias or poor recall in the exposed group (1988).

Till et al. (2001) studied 33 children whose mothers were exposed to organic solvents during pregnancy and matched them with 28 children whose mothers were not exposed to organic solvents during pregnancy. The exposed and non-exposed groups were matched on child’s age (±4 months), gender, ethnicity, and socioeconomic status. The children’s abilities were assessed in the following domains: cognitive abilities using 10 subtests of the Developmental Neuropsychological Assessment (Korkman et al., 1988); language functioning using the Peabody Picture Vocabulary Test (PPVT-III) (Dunn & Dunn, 1997) and the Expressive One-Word Picture Vocabulary Test (revised) (Gardner, 1979); motor functioning using subtests from the Wide Range Assessment of Visual Motor Abilities (Adams & Sheslow, 1995); behavior using the Child Behavior Checklist (Achenbach, 1992, Achenbach, 1991); and attention and impulsivity using the Continuous Performance Test (Connors, 1992). The authors reported that there were significant differences between the exposed and non-exposed groups in language, graphomotor functioning and Total Problem Behavior in 3 to 7 year old children with increased levels of exposure. In this study the examiner herself was not blind to the exposure status of the child although she had an observer who also scored the child being assessed and this person was blind to exposure status. The mothers were not matched for age at which they gave birth. The mothers were exposed a minimum of 8 weeks during pregnancy but exposure was not required over the first trimester of pregnancy when organogenesis occurs.

Perrin et al. (2007) reported on a prospective population-based cohort of 120 offspring whose parents worked in the dry cleaning industry and were exposed to tetrachloroethylene. The authors reported an increased rate of schizophrenia in the exposed offspring. The incidence of schizophrenia in the general population is approximately 1%, however, in their cohort of parental exposure to organic solvents, the incidence was significantly higher at 3.4%. The majority of the offspring with schizophrenia had fathers who were exposed. Perrin et al.
Julvez and Grandjean (2009) conducted a review of the literature on occupational exposure to industrial chemicals during pregnancy. These authors noted the paucity of well controlled cohort studies examining neuropsychological sequela following in utero exposure to organic solvents (Julvez & Grandjean, 2009). Julvez and Grandjean (2009) reviewed the studies noted above in addition to the findings from this study. Based on the literature reviewed, the authors concluded that organic solvent exposure was associated with neurodevelopmental impairment (Julvez & Grandjean, 2009).

1.4.2 Organic Solvent Abuse

Toluene is an aromatic hydrocarbon that is used in paints, glues, and gasoline (Schardein, 2000). Gospe and Zhou (1998) used a rat model of toluene abuse to study the effects of toluene exposure during gestation on the generation and migration of cortical neurons. The brains of pups exposed to toluene had a significantly lower number of neurons within each cortical layer. The investigators concluded that there was an increased risk of abnormal neurogenesis and migration in the rat somatosensory cortex.

Organic solvents have been used intentionally for intoxicating purposes during pregnancy (Hartman, 1995) through gasoline sniffing (Schardein, 2000) or toluene inhalation (Bowen et al., 2005, Bowen & Hannigan, 2006, Costa et al., 2002, Jones & Balster, 1998). The acute toxicity to the central nervous system is well described and there are a number of case reports of highly exposed mothers who abused solvents such as toluene, 1,1,1-trichloroethane, and xylene during pregnancy (Bowen & Hannigan, 2006) and delivered infants with developmental delay and or birth defects (Scheeres & Chudley, 2002, Scheepers & Heussen, 2005).
In humans, authors have suggested that in utero exposure to toluene through maternal inhalation abuse might also be associated with a cluster of facial dysmorphology, termed fetal solvents syndrome or toluene embryopathy (Arnold et al., 1994, Bowen et al., 2005, Bowen & Hannigan, 2006, Costa et al., 2002, Hersh, 1989, Pearson et al., 1994, Toutant & Lippmann, 1979). The phenotypic facial abnormalities (Bowen & Hannigan, 2006) appear to be similar to those seen in fetal alcohol spectrum disorder (FASD) (Arnold et al., 1994, Pearson et al., 1994). Pearson et al. (1994) suggested that there may be a common mechanism of craniofacial teratogenesis for toluene and alcohol, which appears to be a deficiency of craniofacial neuroepithelium and mesodermal components as a result of embryonic cell death.

A report from Japan on two cases of toluene embryopathy indicated that one child (on autopsy at approximately 9 years of age) had marked cortical atrophy and destruction of both temporal lobes with ventricular enlargements, the second child (2 years 5 months, not deceased) had bilateral temporal lobe defects on CT and MRI (Arai et al., 1997). Based on case reports, mothers who had abused toluene during pregnancy were more likely to have children with mental retardation, neuropsychological deficits in cognitive and language domains and behavioral impairment evidenced by inattention and hyperactivity. The exposed children also exhibited cerebellar dysfunction and postnatal growth retardation (Bowen & Hannigan, 2006, Hersh, 1989, Hersh et al., 1985).

The literature on the effects of exposure to other organic solvents for purposes of intoxication is extensive (Filley et al., 2004, Evans & Balster, 1991, Costa et al., 2002, Bowen et al., 2005, Bowen & Hannigan, 2006, Hersh et al., 1985, Harris & Mirza, 2005, Compton et al., 2005, Meggs, 2003, Scheeres & Chudley, 2002). Filley et al. (2004) suggest that the prevalence of solvent abuse is likely underestimated. The lifetime prevalence of inhalant abuse in the United States is estimated at 18% of individuals in the general population and 33.4% of incarcerated individuals. More alarming is the prevalence in young individuals, where it is estimated that 19.9% of eighth grade children have used solvents for the purpose
of intoxication (Sharp & Rosenberg, 1997, Filley et al., 2004). Inhalants appear to be the
drug of choice with minors as they are readily available, legal and inexpensive (Filley et al.,
2004).

1.5 Summary

Organic solvents represent one of the most common types of chemical exposures that occur
al., 2002). The published research to date suggests that exposure to organic solvents during
pregnancy may place the fetus at risk of a multitude of teratogenic insults including birth
defects (Zhu et al., 2006), pregnancy outcome abnormalities (Qin et al., 2008), physiologic
anomalies (Till et al., 2005), and neuropsychological and behavioral deficits (Till et al., 2001,
Qin et al., 2008). Moreover, many women may be unaware that they are pregnant (as they
may be in their first trimester of pregnancy) or they may be unaware of the risks associated
with exposing themselves or their unborn child to organic solvents. Pregnant women may
also not realize that they are being exposed to unsafe limits, however their fetus may suffer
teratogenic consequences (Schardein, 2000, Proposition, 2003).

Standard guidelines have been established with respect to safe organic solvent exposure
limits for the adult in an occupational environment. Empirical data suggest that consequences
of exposure to teratogenic substances may result from levels below those considered safe for
adult exposure. This study aims to determine if there are neuropsychological or behavioral
effects of in utero exposure to organic solvents and whether the dose, maternal symptoms of
toxicity, timing and protective gear utilized minimizes the potential consequences of
exposure.
Chapter 2

Objective, Patients, and Methods

The study design, implementation procedures, patient assessment protocol and all methodology were developed and written by Dionne Laslo-Baker. All grant applications for this research project were written by Dionne Laslo-Baker, referred to in the following sections as the primary investigator.
2 Objective, Patients, and Methods

2.1. Objective

The objective of this study was to compare neuropsychological functioning between children whose mothers were occupationally exposed to organic solvents during pregnancy with a non-exposed matched comparison group. The limitations in previous research were eliminated in this study by: using a prospective design; expanding the age range of the children to 18 months through 8 years eleven months; ensuring that the principal investigator and psychometrists conducting neuropsychological testing were blind to the exposure status of the participants; and conducting a comprehensive neuropsychological and behavioral assessment on the exposed and non-exposed children to determine potential effects associated with organic solvent exposure. Empirical data support the theory that a child’s neuropsychological functioning can be influenced by maternal IQ (Turkheimer, 1991) and maternal education (Geoffroy et al., 2010), therefore, maternal IQ and education were included in the analysis to examine their relationship with the outcome variables.

2.2 Hypothesis

Hypothesis 1

Children exposed in utero to organic solvents will perform more poorly on measures of neuropsychological and behavioral functioning when compared with a matched, non-exposed control group. The areas assessed include:

- Cognition: attention, memory, information processing speed, higher order executive functioning, and intelligence
• Language: receptive and expressive
• Visual – spatial abilities: sensory processing
• Motor and manual dexterity
• Behavior
• Temperament

_Hypothesis 2_

The children in the exposed group will perform more poorly on outcome measures with increased length of gestational exposure; maternal reports of symptoms associated with organic solvent exposure toxicity; maternal detection of odor; and lack of protective gear utilized.

2.3 Participants

Ninety six mothers and their children were recruited from the Motherisk Program at the Hospital for Sick Children in Toronto, Canada. The Motherisk Program is a clinical, research and teaching facility dedicated to antenatal drug, chemical, and disease risk counseling. The program provides evidence-based information and guidance regarding safety or risk of exposure to drugs, chemicals, diseases, radiation, and environmental agents during pregnancy and breastfeeding. In addition to counseling, the Motherisk program is a research facility designed to study the effects of exposure to the agents noted above.

This study included two groups of children and their mothers:

1. An exposed group, which included mothers who had called the Motherisk Program to inquire about safety of exposure to organic solvents in their work environment during their pregnancy, and their offspring.
2. A non-exposed matched comparison group, which included mothers who contacted the Motherisk Program to inquire about safety of exposure to non-teratogenic substances (i.e., acetaminophen, dental x-rays) during their pregnancy. Mothers were eligible to participate in the exposed group if the her pregnancy included at least 8 weeks of exposure to organic solvents that commenced in the first trimester of pregnancy. Exposure during the first trimester is important as this is the period during which the central nervous system (CNS) begins to develop and birth defects related to exposure would have occurred during this important period of in utero development.

The matching criteria in this study were very specific in an attempt to minimize potential confounding variables. A control mother was selected for each exposed mother based on maternal age (within 5 years), child’s age (within 8 months), child’s sex, cigarette use during pregnancy (matched for yes, mother smoked during pregnancy or no, mother did not smoke during pregnancy), and socioeconomic status (annual joint family income divided into 3 categories: $10,000 - $30,000; $31,000 – $50,000; $51,000 and above).

Mothers in either the exposed or non-exposed groups who indicated that they had been exposed to alcohol, drugs of abuse, teratogenic medications, lead, or mercury, or engaged in heavy lifting during their pregnancy, were excluded from the study as these variables are known risks to the developing fetus. Control mothers were also excluded if they had been recruited to other studies in which similar testing batteries were used, as this may invalidate their assessment results. The families who failed to attend their scheduled visits, despite attempts at repeated scheduling, were also excluded from the study (the details of mothers who were excluded are presented in Table 3). The inclusion and exclusion criteria are summarized in Table 2.
Table 2

*Inclusion and Exclusion Criteria for Exposed and Non-Exposed Mothers*

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed to a minimum of one organic solvent over a period of at least 8 weeks of pregnancy with exposure commencing in first trimester</td>
<td>Diagnosed with a medical condition during pregnancy that could cause teratogenic effects</td>
</tr>
<tr>
<td>Contacted the Motherisk Program for counseling regarding safety of exposure to organic solvents during pregnancy between 1989 and 1998</td>
<td>Exposed to a known teratogen such as lead or mercury during pregnancy</td>
</tr>
<tr>
<td>The pregnancy for which she contacted Motherisk resulted in a live birth</td>
<td>Exposed to other chemicals during pregnancy</td>
</tr>
<tr>
<td>Speak English fluently enough to understand and follow instruction for assessment battery</td>
<td>Consumed alcohol during pregnancy</td>
</tr>
<tr>
<td>Resides in Canada</td>
<td>Engaged in heavy lifting during pregnancy</td>
</tr>
<tr>
<td></td>
<td>Traumatic injury during pregnancy that may have placed the fetus at risk</td>
</tr>
<tr>
<td></td>
<td>Recent participation in study in which similar assessment protocols were used</td>
</tr>
<tr>
<td></td>
<td>&quot; Exposed to any organic solvents or other chemicals suspected of being teratogenic</td>
</tr>
</tbody>
</table>

*Note.*  
* Pertains to Exposed Mothers Only  
** Pertains to Non-Exposed Mothers Only

### 2.4 Recruitment Procedure

In order to remain blind to the exposure status of the families, the primary investigator instructed the study coordinator (who was not blind to exposure status) to examine the database of mother’s who contacted the Motherisk Program between 1989 and 1998.
Motherisk counseled over 200,000 women between 1989 and 1998, the study coordinator examined the files of the mothers who had called to inquire on the safety of exposure to organic solvents during that period of time. Two hundred forty two mothers called to inquire about the safety of exposure to organic solvents during that period. At the time of the initial contact with Motherisk (during their pregnancy), the Motherisk counselors used the Motherisk Program Intake Form (Appendix A) to record the reason for their call, current and past pregnancy specifics, as well as exposure information. The exposure information included the following details: maternal occupation, specific type of organic solvent the mother was exposed to, protective gear used during pregnancy, timing of exposure during pregnancy, length of exposure including the daily length and total length up to current point in pregnancy, as well as symptoms associated with organic solvent exposure toxicity. The study coordinator was asked to examine the Motherisk Program Intake Form to examine the details of exposure and determine which mothers met the eligibility criteria for inclusion in the study (refer to table 3 for inclusion / exclusion criteria). The mothers who met the eligibility criteria were contacted by the study coordinator, who followed a standardized text for introduction and discussion about the study (Appendix B). The study coordinator explained that she was following up on the call made to Motherisk during their pregnancy. The coordinator explained that the study currently being conducted was part of a research project toward the principal investigator’s doctoral academic studies. The coordinator asked if the mother would be interested in coming to the Hospital for Sick Children to participate in this follow-up study. The coordinator explained the purpose of the study and reviewed details about their pregnancy, type of exposure, other potential teratogenic exposures during pregnancy, as well as pregnancy outcome using the Motherisk Follow-Up Form (Appendix C) and the Motherisk Pregnancy Follow-Up Form (Appendix D).

From the 242 mothers who were exposed to organic solvents during pregnancy, 194 mothers were excluded from the study (refer to Table 2 for reasons for exclusion). The 48 children and their mothers who met the criteria for inclusion in the study were matched with 48 non-exposed children and their mothers who were eligible for inclusion as a matched comparison.
group. The 48 children, both in the exposed and non-exposed groups, included 16 matched pairs of children between ages 18 months and 2 years 11 months (toddler group) and 32 matched pairs of children between ages 3 years and 8 years 11 months (child group). The two age groups (toddler and child) are differentiated because the neurobehavioral assessment protocol differed to insure age appropriate assessment.
Flowchart For Recruitment

Assessed for eligibility
Exposed mothers and their children
(n=242)

Enrollment of exposed mothers and their children (n=48), matched with non-exposed mothers and their children (n=48)

Exposed Mothers Excluded (n=194)
Not meeting inclusion criteria (n= 58)
Refused to participate (n=50)
Lost to follow-up (n=65)
Other reasons (n=21)

Age appropriate neurobehavioral assessment battery administered to child and mother

Toddler Group matched pairs (n=16)

Child Group matched pairs (n=32)

Figure 1. Summary of participant recruitment and testing.
**Exclusion and Inclusion Details**

**Table 3**

*Sample Exclusion and Inclusion Details*

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number mothers exposed to organic solvents who contacted Motherisk during pregnancy between 1989 – 1998</td>
<td>242</td>
</tr>
<tr>
<td>Total number mother–child pairs who participated in study</td>
<td>48</td>
</tr>
<tr>
<td>Total number mothers who were not contacted</td>
<td>82</td>
</tr>
<tr>
<td>- Lost to follow-up (i.e., number not in service, no listing in telephone directory)</td>
<td>65</td>
</tr>
<tr>
<td>- Not living in Canada</td>
<td>7</td>
</tr>
<tr>
<td>- Maternal thyroid condition</td>
<td>3</td>
</tr>
<tr>
<td>- Mother exposed to other chemicals in addition to organic solvents</td>
<td>4</td>
</tr>
<tr>
<td>- Physician contacted Motherisk, unable to locate mother directly</td>
<td>2</td>
</tr>
<tr>
<td>- Mother called to obtain general information, not specifically regarding a pregnancy</td>
<td>1</td>
</tr>
<tr>
<td>Mothers who refused to participate</td>
<td>50</td>
</tr>
<tr>
<td>Excluded following testing as exposure levels too low</td>
<td>26</td>
</tr>
<tr>
<td>Miscarriage / still birth / child death</td>
<td>9</td>
</tr>
<tr>
<td>Family lived too far away and were unable to travel to Hospital for Sick Children to participate</td>
<td>7</td>
</tr>
<tr>
<td>Family did not show up for appointment and could not be rescheduled</td>
<td>6</td>
</tr>
<tr>
<td>A control match could not be found</td>
<td>3</td>
</tr>
<tr>
<td>Alcohol use during pregnancy</td>
<td>3</td>
</tr>
<tr>
<td>Engaged in heavy lifting at work</td>
<td>2</td>
</tr>
<tr>
<td>Child diagnosed with severe autism</td>
<td>1</td>
</tr>
<tr>
<td>Traumatic insult during pregnancy (severe fall)</td>
<td>1</td>
</tr>
<tr>
<td>Mother could not comprehend English at sufficient level for inclusion</td>
<td>1</td>
</tr>
<tr>
<td>Marijuana use during pregnancy</td>
<td>1</td>
</tr>
<tr>
<td>Mother declined participation as child diagnosed with cystic fibrosis</td>
<td>1</td>
</tr>
<tr>
<td>Child excluded due to physical abuse reported at time of assessment</td>
<td>1</td>
</tr>
</tbody>
</table>
After a mother in either the exposed or matched non-exposed group agreed to participate, the study coordinator mailed a package to the mother containing a cover letter, two consent forms (Appendix E), one for the mother to sign and one to be brought in and signed for the study, as well as an exposure details form (Appendix F).

The families who participated were scheduled to come to the Hospital for Sick Children for the assessment. The families were told that the physician who would initially interview the family was aware of and would review their exposure and pregnancy data with them. They were also told that the principal investigator and psychometrist were unaware of the exposure status of the family and they were asked not to reveal any information regarding pregnancy exposure at any time during their neuropsychological assessment.

The families were initially greeted by the principal investigator or psychometrist who reviewed the consent form with the family to insure a thorough understanding of the study, requirements of participating, and confidentiality. They were also told that a brief summary of the results from their child’s assessment would be mailed to them (Appendix G). The families were again reminded that the principal investigator and psychometrist were intentionally unaware of their exposure status. After informed consent was obtained, the child was seen by a physician who conducted a brief physical and neurological examination. The physician reviewed the details of exposure with the mother’s who had been exposed to organic solvents during pregnancy and confirmed that the matched non-exposed mother’s had not been exposed to any possible teratogens during pregnancy. At that time the physician answered any questions regarding exposure issues.

The primary investigator or psychometrist then met the mother and her child at the assessment laboratory and administered the study tests. To control for order effect, the child’s cognitive abilities (IQ), language functioning and measures of motor development were administered in a random order with each child. The testing time for the children varied in length from 2 to 3 hours. The mother’s intellectual functioning was also assessed and
testing time for mothers was approximately 30 minutes. The child’s assessment battery was administered first and the mother’s assessment was conducted immediately following. Costs incurred by the family for the purpose of participating in the study including transportation, lodging and food were reimbursed by the research grant funding. The child was given a printed award for participating as well as a small toy following completion of the assessment.

The study was prospective in nature as the participant recruitment commenced at the time of the mother’s initial contact with the Motherisk program, before the outcome of the pregnancy was known (live birth, health of the child etc.) and, as noted above, all details related to exposure were recorded at that time. The only component of the study that could be considered retrospective would be the reporting of details of exposure between the time the mother initially contacted Motherisk when she provided extensive exposure and pregnancy details through parturition (time of giving birth).

This study was approved by the Research Ethics Board at the Hospital for Sick Children in Toronto, Ontario Canada. All participants reviewed and signed the Informed Consent form (Appendix E).

### 2.5 Exposure Assessment

The physician recorded information (Appendix H) including specific details about the type of organic solvents involved in the exposure, the type of occupational setting, duration of exposure in pregnancy, any adverse symptoms, type of protective gear used, as well as other safety features including ventilation fans in the work environment. The physician reviewed other details about pregnancy and birth. Information on vitamin supplementation and breastfeeding after birth were also recorded.
2.6 Overview of Assessment Battery

2.6.1 Neuropsychological Assessment

A neuropsychological assessment enables the examiner to objectively measure an individual’s level of functioning in various domains including cognition, emotions, personality, motor functioning, and behavior (Burke, 2009). The results from the assessment can help determine if there is impairment in functioning and quantify the severity of impairment (Burke, 2009). A thorough neuropsychological and behavioral assessment was conducted to obtain gross neuropsychological and behavioral scores as well as sub-test scores that could be examined for more subtle, but potentially important differences between the exposed and non-exposed groups.

The neuropsychological assessment was conducted by the primary investigator or one of 5 psychometrists under the supervision of a registered psychologist (all blind to the exposure status of the child). During the assessment, medical and or psychological issues evidenced were referred for follow-up with the appropriate health care professional.

Each child (both exposed and control) was given an age-appropriate battery of neurodevelopmental tests. All exposed children and their age-matched comparison group were assessed both directly and via parent-completed questionnaires. Two measures of behavioral functioning were administered as behavioral functioning has been shown to be an important issue in earlier studies of exposure to toxic substances (Bailey et al., 2004, Frank et al., 2001, Nulman et al., 2001, Nulman et al., 2004, Sood et al., 2005, Streissguth et al., 1994). A measure of the mother’s cognitive functioning was also obtained during the assessment. Tables 4 and 5 display the neuropsychological assessment battery administered to each child and his or her mother. As this study was one of the first comprehensive examinations on the effects of in utero exposure to organic solvents, a wide range of tests were administered to gain insight into the overall functioning in many areas of
neurocognitive and language development. There was no standardized assessment battery designed to assess potential neuropsychological and behavioral deficits associated with in utero exposure. The principal investigator explored the assessment tools that would optimally assess functioning in the domains outlined for testing hypothesis 1. In doing this, the primary investigator conferred with Speech and Language Therapists to determine the best tests to evaluate language functioning, occupational therapists for manual dexterity, and a psychologist for intellectual and behavioral functioning. The measures used to assess cognitive functioning in the children and the mothers as well as the measures used to assess language functioning in the children all have a mean of 100 and a SD of 15, they include: the Wechsler Primary and Preschool Scale of Intelligence Revised (WPPSI-R), Wechsler Intelligence Scale for Children III (WISC-III), Wechsler Abbreviated Scale of Intelligence for mothers (WASI), Preschool Language Scale 3 (PLS-3), Clinical Evaluation of Language Fundamentals 3 (CELF-3), and the Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI).
### Table 4

**Neuropsychological Assessment Battery: Toddler Group: 18 Months Through 2 Years 11 Months**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Assessment tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive functioning</td>
<td>Bayley Scale of Infant Development: Second Edition (BSID-II)</td>
</tr>
<tr>
<td>Language functioning</td>
<td>PLS-3</td>
</tr>
</tbody>
</table>

**MATERNAL ASSESSMENT**

| Cognitive functioning   | WASI                                                                             |

**PARENT-COMPLETED QUESTIONNAIRES ABOUT THEIR CHILD**

<table>
<thead>
<tr>
<th>Attention/Hyperactivity</th>
<th>Conners’ Parent Rating Scale-Revised (CRS-R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperament</td>
<td>Toddler Temperament Scale (TTS)</td>
</tr>
<tr>
<td>Behavioral functioning</td>
<td>Child Behavior Checklist/2-3 (CBCL/2-3)</td>
</tr>
</tbody>
</table>

### Table 5

**Neurobehavioral Assessment Battery: Child Group: 3 Years Through 8 Years 11 Months**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Assessment tool</th>
<th>Age range for assessment tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive functioning</td>
<td>WPPSI-R</td>
<td>3 years 0 months - 5 years 11 months</td>
</tr>
<tr>
<td></td>
<td>WISC-III</td>
<td>6 years 0 months - 8 years, 11 months</td>
</tr>
</tbody>
</table>
## ASSESSMENT BATTERY

<table>
<thead>
<tr>
<th>Domain</th>
<th>Assessment tool</th>
<th>Age range for assessment tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language functioning</td>
<td>PLS-3</td>
<td>18 months - 5 years, 11 months</td>
</tr>
<tr>
<td></td>
<td>CELF-3</td>
<td>6 years, 0 months - 8 years, 11 months</td>
</tr>
<tr>
<td>Motor abilities</td>
<td>Beery VMI</td>
<td>3 years, 0 months - 8 years, 11 months</td>
</tr>
<tr>
<td></td>
<td>Grooved Pegboard Test</td>
<td>5 years, 0 months - 8 years, 11 months</td>
</tr>
</tbody>
</table>

## MATERNAL ASSESSMENT

| Cognitive functioning  | WASI                             | All mothers |

## PARENT-COMPLETED QUESTIONNAIRES ABOUT THEIR CHILD

<table>
<thead>
<tr>
<th>Attention/Hyperactivity</th>
<th>Conner’s Parent Rating Scale-Revised (CRS-R)</th>
<th>3 years, 0 months - 8 years, 11 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperament</td>
<td>Behavioral Rating Scale (BRS)</td>
<td>3 years, 0 months - 8 years, 11 months</td>
</tr>
<tr>
<td>Behavioral functioning</td>
<td>Child Behavior Checklist/2-3 or /4-18 (CBCL/2-3 or CBCL/4-18)</td>
<td>3 years 0 months - 8 years 11 months</td>
</tr>
</tbody>
</table>
2.6.1.1 Description of Test Battery:

2.6.1.1.1 Toddler Group

2.6.1.1.1.1 Mental and motor development and behavior functioning

The Bayley Scale of Infant Development: Second Edition (BSID-II) (Bayley, 1993) was used to measure the child’s level of development in three domains: the Mental Scale, Motor Scale, and Behavior Rating Scale (BRS). The Mental and Motor Scales assess cognitive, language, personal-social, as well as fine and gross motor development. The BRS assesses behavior during the testing process, which in turn assists in the interpretation of the Mental and Motor Scales.

Based on reports from the test developer the BSID-II has high to moderate reliability. The reliability for the scales are: Mental Scale ranges from 0.75 – 0.93 with a mean of 0.88; Motor Scale ranges from 0.75 – 0.88 with a mean of 0.84; Behavior Rating Scale Total Score ranges from 0.82 – 0.92 with a mean of 0.88. The inter-correlation scores for validity support the construct, predictive, and criterion validity at a moderate to high level (Bayley, 1993).

The Mental Scale assesses areas including memory, habituation, problem solving, early number concepts, generalization, classification, vocalizations, language, as well as social skills. The Motor Scale assesses physical functioning of fine and gross motor muscle groups in activities such as rolling, crawling and creeping, sitting, standing, walking, running, jumping (gross motor activities), prehension, adaptive use of writing equipment, as well as imitation of hand movements (fine motor activities) (Bayley, 1993). The Behavior Rating Scale assesses qualitative features of the child’s behaviour during testing (including orientation engagement toward the task, examiner, and caregiver), emotional regulation, as well as quality of movement.
2.6.1.1.1.2 Language development

The Preschool Language Scale-3 (The PLS-3) (Zimmerman et al., 1992) was used for children ages 18 months through 2 years 11 months. The PLS-3 is composed of two subscales: Auditory Comprehension and Expressive communication, and a Total Language score. The Auditory Comprehension subscale provides information on the child’s receptive language ability, the Expressive Communication subscale provides information on the child’s expressive language ability, and the Total Language score provides information on the child’s overall language functioning. The severity of language deficits is determined by how far the score is from the mean: scores within ±1 SD of the mean are considered to be within normal limits (average), scores between 1 – 1.5 SDs from the mean suggest a mild deficit, scores between 1.5 and 2 SDs from the mean suggest a moderate deficit, and scores greater than 2 SDs from the mean suggest a severe deficit in language functioning.

The test developer reported that the internal consistency reliability for the PLS-3 (Cronbach’s alpha) ranges from 0.47 - 0.86 for Auditory Comprehension, from 0.68 - 0.86 for Expressive Communication, and from 0.74 - 0.92 for the Total Language Score. The inter-rater reliability is 0.98. The concurrent validity correlation results between the PLS and the Clinical Evaluation of Language Fundamentals-Revised (CELF-R) is 0.69 for Auditory Comprehension, 0.75 for Expressive Communication, and 0.82 for Total Language (Zimmerman et al., 1992).

2.6.1.1.1.3 Behavioral functioning

The Child Behavior Checklist (CBCL) (Achenbach, 1992) is a parent-completed questionnaire on which the child is rated for behavioral problems and social competencies. The CBCL for ages 2-3 (CBCL/2-3) was used for the toddler group. The CBCL format employs a 3-step scale for scoring items from 0 to 2 (0 = Not True; 1 = Somewhat True; 2 = Very True/Often True). The questionnaire consists of 100 items on which the parent is asked to rate their child’s behavior over the preceding two-month period.
The items are categorized into six syndrome scales: Anxious/Depressed, Withdrawn, Sleep Problems, Somatic Problems, Aggressive Behavior, and Destructive Behavior (Achenbach, 1992). Raw scores can be converted to standardized summary scores in the form of T scores (Mean = 50, SD = 10) for Internalizing, Externalizing, and Total Problems (Achenbach, 1992). The age-standardized scores can be compared with scale scores from normative samples of children in the same age range.

The test takes approximately 10-15 minutes to complete. This measure is commonly used in both research and clinical settings. Based on reports from the test developer, the test-retest reliability have a mean $r = 0.85$ for the problem scales over an average test-retest period of 7.7 days, the mean inter-parent agreement is $r = 0.63$ across the nine scales (six syndrome and three summary scores) at age 2 and $r = 0.60$ at age 3. The CBCL/2-3 has strong content, construct, and criterion-related validity (Achenbach, 1992).

### 2.6.1.1.2 Child Group

#### 2.6.1.1.2.1 Cognitive functioning

Intellectual ability was measured by using the Wechsler Preschool and Primary Scale of Intelligence - Revised (WPPSI-R) and the Wechsler Intelligence Scale for Children - Third Edition (WISC-III) (Wechsler, 1991, Wechsler, 1989). The WPPSI-R was used for children between the ages of 3 years through 5 years 11 months and the WISC-III was used for children between the ages of 6 years and 8 years 11 months. The results from these tests provide three composite scores: Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FSIQ), which are the combined score of both verbal and performance.

The WPPSI-R consists of 12 subtests, divided into two categories: Performance and Verbal Tests. The following are a description of each subtest (Braken, 2004):

**Performance tests:**
1. Object Assembly - visual-motor integration, visual perception, and fine-motor coordination
2. Geometric Design – visual-motor organization and visual perception
3. Block design - visual integration, visual-motor coordination, and synthesis of part-whole information
4. Mazes – perceptual organization, fine motor skills, and planning
5. Picture Completion – visual organization, attention to detail, and long-term visual memory
6. Animal Pegs - fine motor coordination, memory, attention, and concentration

Verbal tests:
1. Information - long-term memory, verbal fluency, and knowledge of the environment
2. Comprehension - logical reasoning and verbal ability
3. Arithmetic - nonverbal reasoning, understanding of numeric concepts, and visual discrimination
4. Vocabulary - verbal fluency and long-term memory
5. Similarities - verbal fluency, concept formation, and logical reasoning
6. Sentences – memory and verbal fluency

The WISC-III consists of 13 subtests, divided into two categories: Performance and Verbal Tests. The following are a description of each subtest (Braken, 2004, WISC-III, Wechsler, 1991, Sattler, 1992):

Performance tests:
1. Picture Completion - visual organization, attention to detail, and long-term visual memory
2. Coding - visual-motor integration, speed, concentration
3. Picture Arrangement – logical thinking, planning, social knowledge
4. Block design - visual integration, visual-motor coordination, synthesis of part-whole information, and spatial analysis
The WPPSI-R and the WISC-III are widely used in both clinical and research domains. A score of 100 is considered average functioning for a child at a given age. Scores of 85 and 115 corresponds to 1 SD below and above the mean, while scores of 70 and 130 are 2 SDs from the mean (WISC-III, Wechsler, 1991). Approximately two-thirds of all children attain scores between 85 and 115. Clinical classification of IQ scores are as follows: 130+: Very Superior, 120-129: Superior, 110-119: High Average, 90-109: Average, 80-89: Low Average, 70-79: and Borderline, 69-: Intellectually Deficient.

The WPPSI-R manual reported the reliability results for the WPPSI-R Performance, Verbal, and Full Scale IQ domains range from 0.90 - 0.97. Across the nine age groups, the average internal consistency reliabilities are 0.92 for the Performance Scale IQ, 0.95 for the Verbal Scale IQ, and 0.96 for the Full Scale IQ. Test-retest reliabilities for a period of approximately 3 to 7 weeks for Performance are 0.87, Verbal 0.89, and Full Scale IQ 0.91. The WPPSI-R manual indicates that the test has adequate construct, concurrent, and predictive validity. The WPPSI-R was standardized on 1,700 children, 100 boys and 100 girls in each of eight age groups from ages 3 to 7 and one group of 50 boys and 50 girls from 7 years.
The WISC-III manual reported that the three scales have internal consistency reliability coefficients of 0.89 over the whole age range in the standardization group. The average internal consistency reliability coefficients are 0.96 for the Full Scale IQ, 0.95 for the Verbal IQ, and 0.91 for the Performance Scale IQ. The average subtest internal consistency reliabilities range from 0.69 for Object Assembly to 0.87 for Vocabulary and Block Design. Test-retest reliability ranged from 0.87 to 0.94 for IQ scores (Wechsler, 1991, Sattler, 1992).

2.6.1.1.2.2 Language functioning

For children between ages 3 years and 5 years 11 months the Preschool Language Scale - 3 (PLS-3) (Zimmerman et al., 1992) was used (as described earlier in toddler section). For children between the ages of 6 years and 8 years, 11 months the Clinical Evaluation of Language Fundamentals-3 (CELF-3) (Semel et al., 1995).

The CELF-3 provides Receptive and Expressive Language composite scores as well as a Total Language score. The severity of language deficit is determined in the same manner as the PLS-3.

More than 3,300 children, adolescents, and young adults participated in the standardization of the CELF-3. The Manual for the CELF-3 reported that the concurrent validity has been well established. Cronbach’s coefficient alphas for internal consistency were as follows: six year old children, Receptive Language 4.6 (standard error measurement), Expressive Language 3.8, and Total Language 3.2, seven year old children, Receptive Language 4.9, Expressive Language 3.8, and Total Language 3.3, eight year old children, Receptive Language 4.9, Expressive Language 4.0, and Total Language 3.4 (Semel et al., 1995).
2.6.1.1.2.3 Behavioral functioning

The CBCL for ages 4 – 18 (CBCL/4-18) (Achenbach, 1991) was used to assess behavioral functioning. The CBCL/4-18 consists of 118 items that the parent is asked to complete. The measure has eight syndrome scales: Withdrawn, Somatic Complaints, Anxious, Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior.

The test-retest reliability was 0.87 for the Social Competence Scale and 0.89 for the Behavior Problems Scale. The inter-parent correlations range from 0.74 – 0.78 for Social Competence Scales and from 0.65 – 0.75 for the Behavior Problem Scales. The Cronbach’s alpha results for the scales range from 0.46 – 0.93 for boys and 0.54 – 0.93 for girls. The Cronbach’s alpha values for the eight syndrome scales range from 0.62 – 0.92 for boys and 0.66 – 0.92 for girls. The content, construct, and criterion-related validity is strong and has been well documented (Achenbach, 1991).

The Conners Rating Scales-Revised (CRS-R) (Conner, 1997) was used as a second measure of behavioral functioning, this measure is also more specific in assessing symptoms of attention deficit / hyperactivity disorder (ADHD). The CRS-R also evaluates problem behavior including conduct, cognitive, anxiety, as well as social problems. The test is completed by the child’s parent. The Parent Long Form contains 80 questions with 14 subscales: Oppositional, Cognitive Problems/Inattention, Hyperactivity, Anxious/Shy, Perfectionism, Social Problems, Psychosomatic, Conners’ Global Index, Restless-Impulsive, Emotional Lability, ADHD Index, DSM-IV Symptoms subscales, DSM-IV Inattentive, and DSM-IV Hyperactive-Impulsive.

The norms for the CRS-R were based on a sample exceeding 8000 children and adolescents ages 3 – 17 (male and female) in both the United States and Canada. The standardized data were derived from the means and SDs for groups of children both with ADHD and without psychological problems. The test has strong reliability and validity and is commonly used in
the behavioral assessment of children (Goyette et al., 1978). The test authors reported that the coefficient alphas for internal reliability ranged from 0.73 - 0.94 and 0.86 - 0.94 for the short form of the CRS-R, suggesting that the test subscales are accurately measuring their intended constructs. The validity of the CRS-R is also strong (Conner, 1997).

2.6.1.1.2.4 Temperament

Temperament was assessed by the Toddler Temperament Scale (Fullard et al., 1978), or the Behavioral Style Questionnaire (McDevitt & Carey, 1978), depending on the child's age. These are well-established measures for 1-3 or 3-8-year-old children, respectively. Both tests consist of 100 age-appropriate descriptions, which parents score on a 6-point scale from "almost never" to "almost always". Items are scored for nine domains of temperament, derived originally from factor analyses. The nine scales include: activity, regularity of routines, approach/withdrawal, adaptability, intensity, mood, persistence, distractibility, and threshold of response. Scores from individual scales are used to classify children into different temperament style subtypes (i.e., easy, difficult, slow-to-warm-up).

Based on reports from the test author, the test-retest reliability for the Toddler Temperament Scale ranges from 0.69 to 0.89 and from 0.67 to 0.94 for the Behavioral Style Questionnaire. Alpha reliability (internal reliability) for the Toddler Temperament Scale ranges from 0.53 to 0.86 and from 0.47 to 0.80 for the Behavioral Style Questionnaire. Scores on early temperament tests are reportedly stable and predictive of subsequent learning disabilities and behavior problems (Hegvik et al., 1982, McDevitt & Carey, 1978).

2.6.1.1.2.5 Visual perception and motor functioning

The Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI) (Beery, 1997) assesses children’s abilities to integrate and coordinate visual perceptual and motor (finger and hand movement) skills. Visual-motor integration is defined as the degree to
which visual perception and finger-hand movements are well coordinated (Beery, 1997). The test is presented as drawings of geometric forms of increasing difficulty. The child is asked to copy the drawings with paper and pencil. The Beery VMI was standardized on a national sample of 2,512 children/adolescents ranging in age from 2 through 18 years. Validity and reliability measures for the Beery VMI are as follows: test-retest is 0.89, internal consistency (split-half) is 0.88, and interscorer is 0.92 (Beery, 1997).

The Grooved Pegboard Test (Trites, 1989) is a manipulative dexterity test that consists of a board of 25 holes in randomly positioned spots. The child is asked to complete the task as fast as he or she can. This task was used in addition to the Beery VMI as it requires the use of different modes of manual dexterity. Each peg consists of a key along one side that must be rotated appropriately to match and fit in the hole before it can be inserted. The test is used as a measure of complex visual-motor coordination. The Grooved Pegboard Test has been well standardized and has good reliability and validity (Trites, 1989).

2.6.1.1.2.6 Maternal intellectual functioning

Maternal intellectual functioning was determined by using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). This test provides a Verbal IQ (VIQ) score, Performance IQ (PIQ) score as well as a Full Scale IQ (FSIQ) score. Each of the composite scores as well as the Full Scale score has a mean of 100 and a SD of 15. Average reliability coefficient for the FSIQ is 0.98, test-retest reliability for the FSIQ is 0.92, and inter-rater reliability is 0.98 for Vocabulary and 0.99 for Similarities. The test has strong validity and was standardized on 2,245 individuals (Wechsler, 1999).
2.7 Statistical Analysis

Analysis of the data were performed using SPSS Version 20 (SPSS, 2011). In an effort to reduce the possibility of Type II error (false negative), there were no corrections made for multiple comparisons. In addition, because this study was exploratory in nature, a $p$ value of $<0.05$ was used as a cutoff for significance. The results section will be presented in three chapters. The first chapter will cover demographic details, data distribution, developmental milestone attainment of the children, a list maternal occupations, type of organic solvent exposure (for example, toluene versus xylene) and the number of women exposed to each, as well as exposure details such as number of hours exposed, type of protective gear worn and symptoms associated with organic solvent toxicity reported by mothers. The second data chapter will cover results for testing hypothesis 1. The following is a sequential list of the statistics used to examine the data for testing hypothesis 1:

Hypothesis 1: Exposure to organic solvents during in utero development will result in poorer performance on measures of functioning in the following areas: cognition, language, visual perception, motor, behavior, and temperament when compared with a matched comparison group of children whose mothers were not exposed to organic solvents during pregnancy.

1. To check for differences between the exposed and non-exposed groups on both the outcome measures, the Mann-Whitney U was used when the sample size was less than 16, otherwise the independent-samples $t$ test was used. The sample size for each assessment tool varied depending on how broad the age range was for the test or whether test scores could be amalgamated, resulting in a larger sample size for that outcome variable. For example, the IQ scores from the WISC III and the WPPSI-R were amalgamated and termed: Verbal IQ, Performance IQ and Full Scale IQ (as opposed to WISC III Verbal IQ, WPPSI-R Verbal IQ etc.).

2. To check the distribution of test scores found to be significantly different between the exposed and non-exposed groups, the Q-Q plot and histogram were used to examine the sample distribution.
3. Those continuous variables that were significantly different between the exposed and non-exposed children on the Mann-Whitney U or the independent-samples t test were included in a Pearson product-moment correlation analysis to assess their correlation with maternal variables.

4. To examine whether exposure status predicted lower outcome scores, a hierarchical linear regression approach was used. Scores showing significant group differences in the Mann Whitney U or independent-samples t tests were selected as the outcome variables for this analysis. The predictor variables were maternal FSIQ, maternal education, and exposure status. Maternal education recorded as the highest educational level achieved by the mother. Education was ranked from 1 through 5 (1: elementary school completion, 2: high school, 3: college, 4: university degree, and 5: graduate training). The maternal variables were entered first, followed by exposure status, to determine whether it contributed above and beyond the maternal variables.

The third data chapter will cover results for testing hypothesis 2. For all analyses testing hypothesis 2, only the data from the exposed children were included as the independent variables for hypothesis 2 were pertinent only to the exposed sample. The following is a sequential list of the statistics used to examine the data testing hypothesis 2:

Hypothesis 2: Factors including the hours of exposure per week, length of gestational exposure, detection of organic solvent odor during exposure, lack of protective gear utilized, and total number of symptoms associated with organic solvent toxicity during in utero development will result in poorer performance on the measures of neuropsychological and behavioral functioning.

1. To assess the relationship with the outcome variables (using those that were significantly different between the two groups in hypothesis 1) and exposure variables that were categorical in nature (barrier use, and detection of odor), the Mann Whitney U test was employed.
2. A correlation matrix was used to determine which outcome variables (significantly different between the two groups in hypothesis 1) were significantly correlated with exposure variables that were continuous in nature, which included: duration (total number of hours of exposure per week), total length of gestational exposure, and total number of symptoms associated with organic solvent exposure toxicity reported by the mother.

The independent and dependent variables for the study are outlined below:

**Independent Variables:**

- Exposure status (exposed or not exposed to organic solvents);
- Hours of exposure per week
- Length of gestational exposure
- Protective gear worn by mother during in utero exposure to organic solvents
- Maternal reports of symptoms associated with organic solvent exposure toxicity
- Maternal IQ and education

**Dependent Variables:**

- Neuropsychological outcome scores
- Behavioral outcome scores
Chapter 4

Results: Descriptive Statistics
4.1 Results: Descriptive Statistics

4.1.1 Overview

Independent-sample $t$ test including demographic data, pregnancy details, and developmental milestone achievements are presented in Table 5. The exposed and non-exposed mothers differed on several pregnancy and post-pregnancy variables (see Table 6): significantly more exposed mothers reported taking vitamin/folic acid supplements during pregnancy, $t(62) = .99, p = .05$; although both the exposed and non-exposed mothers were within the normal range for weight prior to their pregnancy and at the time of delivery, the exposed mothers weighed significantly less than their matched controls at both points, $t(-2.37) = .53, p = .03$; $t(-2.93) = 53, p = .004$; the 5 minute Apgar score for the exposed group was significantly higher (better score) than the non-exposed group, $t(1.08) = 14, p = .01$, however, there were only 5 mother’s in each group who remembered or had access to Apgar scores; and exposed mothers reported breast feeding for a longer period than the non-exposed group, $t(1.03) = 62, p = .04$.

Table 7 lists the occupations of the exposed and control mothers. Mothers in the exposed group reported being exposed to 24 types of organic solvents (see Table 8) between 1 and 40 hours per week (mean $24\pm15hr$) and between 8 and 40 weeks [mean $32\pm10wks$] of their pregnancy (see Table 9). The most commonly reported occupations were laboratory technician, factory worker, followed by graphic design. The most common type of organic solvent exposure was to toluene. Both the type of solvent exposure and the occupations reported are consistent with the literature. All women in the exposed group had been exposed to organic solvents during most of their first trimester of pregnancy. Seventy two percent of the exposed mothers reported using protective equipment and less than 2 % of the exposed mothers reported experiencing symptoms associated with organic solvent exposure toxicity.
Table 6

Demographic and Developmental Milestones: Exposed and Non-Exposed

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Non-Exposed</th>
<th>t</th>
<th>df</th>
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<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Child age at testing</td>
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<td>23.45</td>
<td>69.47</td>
<td>22.61</td>
</tr>
<tr>
<td>Maternal age at confinement (years)</td>
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<td>4.19</td>
<td>31.17</td>
<td>3.92</td>
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<td>Maternal age at testing</td>
<td>36.53</td>
<td>5.23</td>
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</tr>
<tr>
<td>Maternal education*†</td>
<td>3.35</td>
<td>.96</td>
<td>3.52</td>
<td>.77</td>
</tr>
<tr>
<td>Paternal education*†</td>
<td>3.50</td>
<td>1.14</td>
<td>3.22</td>
<td>.98</td>
</tr>
<tr>
<td>Socioeconomic status*‡</td>
<td>2.81</td>
<td>.40</td>
<td>2.81</td>
<td>.40</td>
</tr>
<tr>
<td>Vitamin Use/Folic Acid* (yes/no)</td>
<td>.88</td>
<td>.34</td>
<td>.78</td>
<td>.42</td>
</tr>
<tr>
<td>Pre-pregnancy weight*</td>
<td>62.30</td>
<td>13</td>
<td>72.41</td>
<td>17.95</td>
</tr>
<tr>
<td>Maternal weight at delivery*</td>
<td>76.08</td>
<td>11.09</td>
<td>87.56</td>
<td>16.95</td>
</tr>
<tr>
<td>Length of labour (hours)</td>
<td>13.46</td>
<td>18.87</td>
<td>11</td>
<td>9.42</td>
</tr>
<tr>
<td>Fetal distress (yes/no)</td>
<td>1.63</td>
<td>.83</td>
<td>1.72</td>
<td>.89</td>
</tr>
<tr>
<td>Neonatal ICU (yes/no)</td>
<td>.16</td>
<td>.37</td>
<td>.13</td>
<td>.35</td>
</tr>
<tr>
<td>Birth defects (yes/no)</td>
<td>.03</td>
<td>1.77</td>
<td>.03</td>
<td>.18</td>
</tr>
<tr>
<td>Length breastfeeding (months)</td>
<td>9.88</td>
<td>17.08</td>
<td>6.55</td>
<td>4.48</td>
</tr>
<tr>
<td>Apgar (1 min)</td>
<td>8.55</td>
<td>1.13</td>
<td>7.63</td>
<td>2.0</td>
</tr>
<tr>
<td>Apgar (5 min)*</td>
<td>9.45</td>
<td>.50</td>
<td>8.75</td>
<td>1.99</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.31</td>
<td>.67</td>
<td>3.43</td>
<td>.58</td>
</tr>
<tr>
<td></td>
<td>Exposed</td>
<td>Non-Exposed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.44</td>
<td>2.28</td>
<td>39.28</td>
<td>1.76</td>
</tr>
<tr>
<td>Age solids introduced</td>
<td>5.41</td>
<td>2.47</td>
<td>4.72</td>
<td>1.40</td>
</tr>
<tr>
<td>Feeding problems (yes/no)</td>
<td>.16</td>
<td>.37</td>
<td>.13</td>
<td>.35</td>
</tr>
<tr>
<td>Height (time of testing-cm)</td>
<td>114.74</td>
<td>13.67</td>
<td>113.24</td>
<td>17.32</td>
</tr>
<tr>
<td>Weight (time of testing-kg)</td>
<td>23.09</td>
<td>9.28</td>
<td>22.41</td>
<td>8.26</td>
</tr>
<tr>
<td>Head Circumference (time of testing-cm)</td>
<td>51.73</td>
<td>2.23</td>
<td>53.81</td>
<td>12.10</td>
</tr>
<tr>
<td>Lift head (week)</td>
<td>9.54</td>
<td>3.50</td>
<td>10.61</td>
<td>2.80</td>
</tr>
<tr>
<td>Sit (week)</td>
<td>24.97</td>
<td>4.10</td>
<td>23.98</td>
<td>4.37</td>
</tr>
<tr>
<td>Crawl (week)</td>
<td>37.57</td>
<td>21.17</td>
<td>36.12</td>
<td>13.68</td>
</tr>
<tr>
<td>Stand (week)</td>
<td>36.76</td>
<td>5.64</td>
<td>36.96</td>
<td>6.47</td>
</tr>
<tr>
<td>First word (week)</td>
<td>36.13</td>
<td>6.81</td>
<td>38.24</td>
<td>18.94</td>
</tr>
<tr>
<td>Walk (week)</td>
<td>47.28</td>
<td>6.23</td>
<td>47.40</td>
<td>9.22</td>
</tr>
</tbody>
</table>

*Note.* *p*<.05; **p**<.01; ***p***<.001

*1 Completed up to (1) elementary, (2) high school, (3) college, (4) university, (5) graduate school
Table 7

*List of Maternal Occupations for the Exposed and Non-Exposed Groups*

<table>
<thead>
<tr>
<th>Exposed</th>
<th>Non-exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab technician (8)</td>
<td>Teacher (5)</td>
</tr>
<tr>
<td>Factory worker (4)</td>
<td>Stay at home mother (4)</td>
</tr>
<tr>
<td>Graphic designer (3)</td>
<td>Nurse (2)</td>
</tr>
<tr>
<td>Photo lab work (2)</td>
<td>Social worker (2)</td>
</tr>
<tr>
<td>Conservator (2)</td>
<td>Sales manager (2)</td>
</tr>
<tr>
<td>Funeral director / embalmer (2)</td>
<td>Systems training manager</td>
</tr>
<tr>
<td>Chemical technologist</td>
<td>Office worker</td>
</tr>
<tr>
<td>Hair stylist / color technician</td>
<td>Day care teacher</td>
</tr>
<tr>
<td>Interior design consultant</td>
<td>Coordinator for pharmaceutical company</td>
</tr>
<tr>
<td>Painter</td>
<td>Payroll administrator</td>
</tr>
<tr>
<td>Salon receptionist</td>
<td>Circulation manager</td>
</tr>
<tr>
<td>Science teacher</td>
<td>Secretary</td>
</tr>
<tr>
<td>Aesthetician</td>
<td>Accountant</td>
</tr>
<tr>
<td>Industrial laundry worker</td>
<td>Law clerk</td>
</tr>
<tr>
<td>Chemist</td>
<td>Legal secretary</td>
</tr>
<tr>
<td>Carpenter</td>
<td>Receptionist / dental assistant</td>
</tr>
<tr>
<td>Electrical company worker</td>
<td>Computer programmer</td>
</tr>
<tr>
<td></td>
<td>Pediatric Assistant</td>
</tr>
<tr>
<td></td>
<td>Marketing Assistant</td>
</tr>
<tr>
<td></td>
<td>Book Keeper</td>
</tr>
<tr>
<td></td>
<td>Financial Planner</td>
</tr>
<tr>
<td></td>
<td>Lawyer</td>
</tr>
<tr>
<td>Chemical</td>
<td>Number of women exposed</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Toluene</td>
<td>12</td>
</tr>
<tr>
<td>Xylene</td>
<td>10</td>
</tr>
<tr>
<td>Ethanol</td>
<td>7</td>
</tr>
<tr>
<td>Acetone</td>
<td>6</td>
</tr>
<tr>
<td>Methanol</td>
<td>5</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>4</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>4</td>
</tr>
<tr>
<td>Mineral spirits</td>
<td>4</td>
</tr>
<tr>
<td>isopropyl alcohol</td>
<td>4</td>
</tr>
<tr>
<td>benzalkonium-chloride</td>
<td>3</td>
</tr>
<tr>
<td>acrylic resin</td>
<td>3</td>
</tr>
<tr>
<td>methylene chloride</td>
<td>3</td>
</tr>
<tr>
<td>Hexane</td>
<td>3</td>
</tr>
<tr>
<td>trichloroethylene</td>
<td>3</td>
</tr>
<tr>
<td>Phenol</td>
<td>2</td>
</tr>
<tr>
<td>propylene glycol</td>
<td>2</td>
</tr>
<tr>
<td>monomethyl ether acetate</td>
<td>2</td>
</tr>
<tr>
<td>triethylene glycol</td>
<td>2</td>
</tr>
<tr>
<td>benzyl alcohol</td>
<td>2</td>
</tr>
<tr>
<td>naphthoxypoly-oxyethylene</td>
<td>2</td>
</tr>
<tr>
<td>1,1,1 - trichloroethane</td>
<td>2</td>
</tr>
<tr>
<td>Methyl-ethyl ketone</td>
<td>2</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>2</td>
</tr>
<tr>
<td>t-butanol</td>
<td>2</td>
</tr>
</tbody>
</table>

*Note.* *Some mothers were exposed to more than one solvent.*
Table 9

*Exposure Details*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours of exposure during pregnancy</td>
<td>742</td>
</tr>
<tr>
<td>Weekly hours of exposure</td>
<td>24.5</td>
</tr>
<tr>
<td>Number of weeks exposed (between 8 – 40)</td>
<td>32</td>
</tr>
<tr>
<td>Number of symptoms (ranging from 1 – 5)</td>
<td>0.81</td>
</tr>
<tr>
<td>Detection of odor (no / yes)</td>
<td>0.19</td>
</tr>
<tr>
<td>Protective gear worn (no / yes)</td>
<td>0.72</td>
</tr>
</tbody>
</table>
Chapter 5

Results: Hypothesis 1
5.1 Results: Hypothesis 1

5.1.1 Overview

The Toddler and Child Group data are presented separately as the test battery employed was developmentally appropriate for the corresponding age group but the test data could not be analyzed together since the tests measure different domains. The necessity to use developmentally appropriate assessment tools resulted in a smaller $n$ for some tests. The WISC III and WPPSI-R IQ scores were amalgamated and are termed Verbal IQ, Performance IQ, and Full Scale IQ. The PLS-3 and CELF-3 scores were amalgamated and are termed Receptive Language, Expressive Language and Total Language. This amalgamation was done so that the sample size or each of these variables was larger.

All global IQ and language scores will be presented, otherwise only significant test and subtest scores will be presented in the following sections. Before interpreting the results of the independent-samples $t$ test, the assumption of homogeneity of variance was checked and the appropriate statistic is reported.

The sample size for the Toddler Group was 16 matched pairs of exposed and non-exposed children and their mothers. The results from the Toddler Group are exploratory in nature and show only trends as the sample size was too small to warrant conclusive statements. The sample size for the Child Group was 32 matched pairs of exposed and non-exposed children and their mothers.
5.1.1.1 Toddler Group: Comparison of Exposed and Non-Exposed Children

The Mann Whitney $U$ test was used to assess the differences between the exposed and non-exposed children on the outcome variables for the toddler group. Table 10 presents the scores for the BSID and the PLS-3. The exposed children performed significantly lower than their matched comparison group on the PLS-3 Auditory Comprehension raw score $U = 72.50$, $p = .04$. The results from the CBCL/2-3 scores indicated that, compared to the non-exposed group, the exposed children had significantly higher scores in the following domains: anxiety and depression $U = 33.00$, $p = .04$; and destructive behavior $U = 23.00$, $p = .03$. Although the following variables were not significantly different between the exposed and non-exposed children, they show a tendency close to significance. The exposed children displayed a tendency to show more problems on the following scales: PLS-3 Total age equivalent score $U = 75.00$, $p = 0.07$; Toddler Temperament Scale activity mean score $U = 75.50$, $p = 0.05$. The unexposed control children displayed a tendency for higher scores on the CBCL/2-3 sleep problems T score $U = 27.00$, $p = .07$. 
Table 10

*Group Differences Between the Exposed and Non-Exposed Children (Toddler Group)*

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Exposed mean rank</th>
<th>Non-exposed mean rank</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSID: Mental Scale MDI&lt;sup&gt;1&lt;/sup&gt;</td>
<td>15.44</td>
<td>17.56</td>
<td>111.00</td>
</tr>
<tr>
<td>BSID: Motor Scale PDI&lt;sup&gt;2&lt;/sup&gt;</td>
<td>16.81</td>
<td>16.19</td>
<td>123.00</td>
</tr>
<tr>
<td>BSID: Behavior Total Score percentile</td>
<td>15.47</td>
<td>15.53</td>
<td>112.00</td>
</tr>
<tr>
<td>PLS Auditory Comprehension scaled score</td>
<td>14.78</td>
<td>18.22</td>
<td>100.5</td>
</tr>
<tr>
<td>PLS Auditory Comprehension raw score</td>
<td>13.03</td>
<td>19.97</td>
<td>72.50*</td>
</tr>
<tr>
<td>PLS Expressive Communication scaled score</td>
<td>15.03</td>
<td>17.03</td>
<td>104.50</td>
</tr>
<tr>
<td>PLS Total scaled score</td>
<td>14.47</td>
<td>17.63</td>
<td>95.50</td>
</tr>
<tr>
<td>CBCL Anxious Depressed T score</td>
<td>12.33</td>
<td>9.00</td>
<td>33.00*</td>
</tr>
<tr>
<td>CBCL Destructive Behaviour T score</td>
<td>13.44</td>
<td>8.09</td>
<td>23.00*</td>
</tr>
</tbody>
</table>

*Note. 1*MDI – Mental Developmental Index  
*2*PDI – Psychomotor Development Index
5.1.2 Child Group Results: Statistical Analysis for Hypothesis 1

5.1.2.1 Cognitive and language functioning

The Independent-samples $t$ test and the Mann Whitney $U$ test were conducted to examine whether there were statistically significant differences on outcome measures between children whose mothers were exposed to organic solvents during pregnancy and children whose mothers were not exposed to organic solvents during pregnancy. When the homogeneity of variance assumption was not met, the adjusted $t$ statistic and $df$ are reported.

Table 11 presents the results of the independent-samples $t$ test for the cognitive and language outcome scores for the exposed and non-exposed groups. Recall that all global IQ and language scores will be presented, otherwise only significant test and subtest scores will be presented in the following sections. The exposed children scored significantly lower than their matched non-exposed cohort on the following primary outcome variables: Verbal IQ $t(62) = 13.46, p = .02$ (medium effect size, $d = .59$); WISC-III Digit Span $t(19) = 1.98, p = .05$ (large effect size, $d = .96$); CELF-3 Receptive Language percentile $t(26.48) = -2.50, p = 0.02$ (large effect size, $d = .97$); CELF-3 Expressive Language percentile $t(26.86) = -2.17, p = 0.04$ (large effect size, $d = .84$). Although the following variables were not significantly different between the exposed and non-exposed children, they show a trend. The exposed children displayed a tendency to show poorer outcome on the following scales: Full - Scale IQ $t(62) = 12.49, p = .07$; WISC-III: Digit Span Reverse (scaled score) $t(19) = 1.98, p = .06$; Information (scaled score) $t(35) = 1.98, p = .10$; Expressive Language (standard score) $t(60) = 16.41, p = .08$, and Total Language $t(60) = 15.45, p = .1$; CELF-3 Recalling Sentences (standard score) $t(35) = 1.46, p = .06$.

Table 12 presents the results of the Mann Whitney $U$ test for the outcome scores for the exposed and non-exposed groups. WPPSI: Verbal IQ $U = 49.50, p = .04$; Information:
(scaled score) $U = 44.50, p = .02$; Vocabulary (scaled score) $U = 50.00, p = .04$; Sentences $U = 24.00, p = .04$; PLS-3: Auditory Comprehension (scaled score) $U = 34.00, p = .02$; Auditory Comprehension age equivalent $U = 33.50, p = .02$. The following results are not significant, but suggest a tendency toward significance: WPPSI-R Similarities (scaled score) $U = 56.50, p = .09$; PLS-3: Total T (scaled score) $U = 56.50, p = .10$; standard score of total standards scores $U = 47.00, p = .09$; age equivalent T score (total test) $U = 55.50, p = .08$.

**Table 11**

*Group Differences Between the Exposed and Non-Exposed Children (Child Group)*

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Exposed</th>
<th>Non-exposed</th>
<th>$t$</th>
<th>df</th>
<th>$d$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$</td>
<td>$SD$</td>
<td>$M$</td>
<td>$SD$</td>
<td></td>
</tr>
<tr>
<td>Verbal IQ score</td>
<td>108.31</td>
<td>13.46</td>
<td>116.25</td>
<td>13.93</td>
<td>-2.32*</td>
</tr>
<tr>
<td>Performance IQ score</td>
<td>107.53</td>
<td>15.02</td>
<td>108.38</td>
<td>12.48</td>
<td>-2.44</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>108.41</td>
<td>12.49</td>
<td>114.28</td>
<td>12.61</td>
<td>-1.87</td>
</tr>
<tr>
<td>WISC Digit Span scaled score</td>
<td>10.71</td>
<td>1.98</td>
<td>12.43</td>
<td>1.65</td>
<td>-2.10*</td>
</tr>
<tr>
<td>Receptive language</td>
<td>112.75</td>
<td>15.08</td>
<td>117.14</td>
<td>14.45</td>
<td>-1.15</td>
</tr>
<tr>
<td>Expressive language</td>
<td>109.19</td>
<td>16.41</td>
<td>115.57</td>
<td>11.48</td>
<td>-1.78</td>
</tr>
<tr>
<td>CELF recalling sentences percentile</td>
<td>66</td>
<td>31.88</td>
<td>86.44</td>
<td>15.59</td>
<td>-2.50*</td>
</tr>
<tr>
<td>CELF expressive language percentile</td>
<td>64.79</td>
<td>30.70</td>
<td>81.94</td>
<td>15.43</td>
<td>-2.17*</td>
</tr>
</tbody>
</table>

*Note.* *p*<.05; **p**<.01
Table 12

*Group Differences Between the Exposed and Non-Exposed Children (Child Group)*

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Exposed mean rank</th>
<th>Non-exposed mean rank</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPPSI-R VIQ</td>
<td>10.81</td>
<td>16.96</td>
<td>49.50*</td>
</tr>
<tr>
<td>WPPSI-R PIQ</td>
<td>13.69</td>
<td>14.29</td>
<td>87.00</td>
</tr>
<tr>
<td>WPPSI-R FSIQ</td>
<td>11.62</td>
<td>16.21</td>
<td>60.00</td>
</tr>
<tr>
<td>WPPSI-R Information sub-test scaled score</td>
<td>10.42</td>
<td>17.32</td>
<td>44.50*</td>
</tr>
<tr>
<td>WPPSI-R Vocabulary sub-test scaled score</td>
<td>10.85</td>
<td>16.93</td>
<td>50.00*</td>
</tr>
<tr>
<td>WPPSI-R Sentences sub-test raw score</td>
<td>7.50</td>
<td>13.15</td>
<td>24.00*</td>
</tr>
<tr>
<td>PLS-3 Auditory Comprehension scaled score</td>
<td>9.62</td>
<td>16.67</td>
<td>34.00*</td>
</tr>
<tr>
<td>PLS-3 Expressive Communication scaled score</td>
<td>11.12</td>
<td>15.04</td>
<td>47.50</td>
</tr>
<tr>
<td>PLS-3 Total scaled score</td>
<td>10.65</td>
<td>15.54</td>
<td>53.50</td>
</tr>
<tr>
<td>PLS-3 Auditory Comprehension age equivalent</td>
<td>9.58</td>
<td>16.71</td>
<td>33.50*</td>
</tr>
</tbody>
</table>

*Note.* *p*<.05

The distribution of test scores for cognitive and language variables that were significantly different between the exposed and non-exposed child groups are presented in Appendix I.
5.1.2.2 Behavioral Functioning, Temperament, and Motor Skills

Table 13 presents the results for the independent-samples t test on the behavior and motor outcome variables. The results suggest that exposed children scored significantly more clinical symptoms than their matched comparison group on the following measures of Behavioral Functioning: CRS-R DSM-IV symptom subscales raw score $t(32.24) = 9.33, p = .000$ (large effect size, $d = 1.52$) and T score $t(56) = 10.07, p = .02$ (medium effect size, $d = .65$). The exposed children performed significantly lower than exposed on the Grooved Pegboard, non-dominant hand $t(32) = .53, p = .004$ although the sample size was small ($n = 17$) and the effect size was low ($d = .09$). The following results are not significant but display a tendency toward significance. The CBCL/4-18: Total T score $t(57) = 53.03, p = .07$; Internalizing T score $t(57) = 10.14, p = .07$; Somatizing T $t(57) = 6.73, p = .07$; the Conners Rating Scale Hyperactivity / Impulsivity Index (raw score) $t(56) = 5.25, p = .07$; Behavioral Style Questionnaire Activity level $t(56) = 0.61, p = .09$; and the Grooved Pegboard dominant hand $t(32) = 0.61, p = .09$.

Table 13
Group Differences Between the Exposed and Non-Exposed Children (Child Group)

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Exposed</th>
<th>Non-exposed</th>
<th>t</th>
<th>df</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>CRS DSM Criteria raw score</td>
<td>14.14</td>
<td>9.33</td>
<td>3.93</td>
<td>3.02</td>
<td>5.69***</td>
</tr>
<tr>
<td>CRS DSM Criteria t score</td>
<td>54.4</td>
<td>10.07</td>
<td>48.93</td>
<td>6.94</td>
<td>2.42*</td>
</tr>
<tr>
<td>Grooved pegboard non-dominant hand</td>
<td>0.45</td>
<td>0.53</td>
<td>-0.17</td>
<td>0.63</td>
<td>3.10***</td>
</tr>
</tbody>
</table>

Note. *p<.05; **p<.01; ***p<.001
The distribution of test scores for behavioral functioning, temperament, and motor skills variables that were significantly different between the exposed and non-exposed child groups are presented in Appendix J.

5.1.2.3 Pearson Product-Moment Correlation Analysis to Assess the Relationship Between Maternal FSIQ, Maternal Education and the Outcome Variables

Pearson product-moment correlations were computed to examine the relationship between maternal factors (IQ and education) and the outcome variables that showed significant group differences in the previous analysis (Mann Whitney $U$ and independent-samples $t$ test) (see Table 14). Those variables that were not significantly correlated with maternal IQ and education but were significant in the independent-samples $t$ test or Mann Whitney $U$ test were not analyzed using regression as the correlation analysis already indicated that the maternal factors were not significantly associated with those particular outcome variables.

Table 14
Correlation Matrix Between Maternal Variables and Child Outcome Variables (showing significant correlations only)

<table>
<thead>
<tr>
<th></th>
<th>1.00</th>
<th>2.00</th>
<th>3.00</th>
<th>4.00</th>
<th>5.00</th>
<th>6.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Maternal Full Scale IQ</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Maternal Education</td>
<td>0.37*</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Child Verbal IQ (combined WPPSI-R and WISC-III Verbal IQ scores)</td>
<td>0.41**</td>
<td>0.32**</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. CELF expressive language percentile</td>
<td>0.52**</td>
<td>0.41*</td>
<td>0.66**</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.1.3 Maternal Full Scale IQ and Exposure Status Predicting Outcome Variables

The correlation analysis revealed variables that were significantly correlated with maternal FSIQ, maternal education, and exposure status. When the dependent variable was significantly correlated with maternal factors as well as exposure status, the regression analysis served to assess which variable was the stronger predictor of poorer performance on the outcome variable. Maternal FSIQ, maternal education, and exposure status served as predictors for the regression. The dependent variables included child Verbal IQ, WPPSI-R VIQ, and the CELF Expressive Language and CELF Recalling Sentences Percentile Ranks. Maternal FSIQ and Maternal Education were added in the first step of the regression analysis and exposure status in the second step. The initial results showed that maternal education was not a significant predictor and it was removed from the analysis. With only maternal FSIQ and exposure status in the model 16% of the variance in Child Verbal IQ was explained by Maternal FSIQ while exposure status accounted for an additional 6% (refer to Table 15). For WPPSI-R VIQ, 27% of the variance was accounted for by Maternal FSIQ while an additional 9% of the variance was accounted for by exposure status (refer to Table 16). For CELF Recalling Sentences Percentile 19% of the variance was explained by Maternal FSIQ while Exposure Status accounted for an additional 20% (refer to Table 17). For CELF Expressive Language 27% of the variance was accounted for by Maternal FSIQ while an additional 17% was accounted for by exposure status (refer to Table 18).
### Table 15

**Predicting Child Verbal IQ**

<table>
<thead>
<tr>
<th>Step</th>
<th>Independent variable</th>
<th>β</th>
<th>$R^2$</th>
<th>Δ $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Maternal full scale IQ</td>
<td>0.41**</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>Exposure status</td>
<td>0.25*</td>
<td>0.23</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Note.* *p<.05,** *p<.005

### Table 16

**Predicting WPPSI-R VIQ**

<table>
<thead>
<tr>
<th>Step</th>
<th>Independent variable</th>
<th>β</th>
<th>$R^2$</th>
<th>Δ $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Maternal full scale IQ</td>
<td>0.41*</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>Exposure status</td>
<td>0.31</td>
<td>0.35</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Note.* *p<.05

### Table 17

**Predicting CELF Recalling Sentences Percentile**

<table>
<thead>
<tr>
<th>Step</th>
<th>Independent variable</th>
<th>β</th>
<th>$R^2$</th>
<th>Δ $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Maternal full scale IQ</td>
<td>0.48**</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>Exposure status</td>
<td>0.45**</td>
<td>0.40</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Note.* *p<.05,** *p<.005
### Table 18

*Predicting CELF Expressive Language Percentile*

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>$\beta$</th>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal full scale IQ</td>
<td>0.55**</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure status</td>
<td>0.42**</td>
<td>0.44</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Note.* $^*p<.05$, $^{**}p<0.05$
Chapter 6

Results: Hypothesis 2
6.1 Results: Hypothesis 2

6.1.1 Child Group Results: Statistical Analysis for Hypothesis 2

Table 19 presents the independent sample $t$ test results for differences in maternal IQ and maternal education. There were no significant differences on the maternal variables between the exposed and non-exposed mothers.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Exposed</th>
<th>Non-exposed</th>
<th>$t$</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Verbal IQ</td>
<td>104.63</td>
<td>110.63</td>
<td>-1.92</td>
<td>60</td>
</tr>
<tr>
<td>Maternal Performance IQ</td>
<td>110.70</td>
<td>109.47</td>
<td>.42</td>
<td>60</td>
</tr>
<tr>
<td>Maternal Full Scale IQ</td>
<td>111.41</td>
<td>108.90</td>
<td>-.84</td>
<td>60</td>
</tr>
<tr>
<td>Maternal Education</td>
<td>3.59</td>
<td>3.44</td>
<td>.88</td>
<td>62</td>
</tr>
</tbody>
</table>

6.1.1.1 Mann Whitney U test for dichotomous variables

The Mann Whitney $U$ test was used to check for differences on the outcome scores that showed significant group differences in the previous analysis for hypothesis 1 (Mann Whitney $U$ and independent-samples $t$ test) and maternal reports of detecting odor and reported symptoms associated with toxicity. The children whose mothers reported detecting
odor performed significantly lower on their Verbal IQ score $U = 36.00, p = .04$. There were no significant differences between barrier use and outcome scores.

6.1.1.2 The Relationship Between Maternal Exposure and Significant Outcome Variables (continuous variables)

A correlation matrix was used to determine which outcome variables (using those that were significantly different between the two groups in hypothesis 1) were significantly correlated with maternal exposure variables. The maternal exposure variables that were continuous in nature included: duration (total number of hours of exposure per week), total length of gestational exposure, protective gear worn, and maternal reports of symptoms associated with organic solvent exposure toxicity. The correlation matrix (Table 20) displays only those variables that were significantly correlated. Duration of exposure was significantly correlated with higher ratings on the Conners Rating Scale Hyperactivity / Impulsivity Index (raw score) and T score. Total number of symptoms associated with organic solvent toxicity reported was significantly correlated with poorer performance on the Grooved Pegboard non-dominant hand scores.
Table 20

*Relationship Between Outcome Variables Significantly Different in Hypothesis 1 and Maternal Exposure Variables (continuous variables)*

<table>
<thead>
<tr>
<th></th>
<th>1.00</th>
<th>2.00</th>
<th>3.00</th>
<th>4.00</th>
<th>5.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Duration (total hours exposure per week)</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Total # of symptoms</td>
<td>0.08</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. CRS DSM Criteria raw score</td>
<td>0.43*</td>
<td>0.40*</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. CRS DSM Criteria t score</td>
<td>0.39*</td>
<td>0.36</td>
<td>0.89**</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>5. Grooved Pegboard non dominant hand</td>
<td>0.01</td>
<td>-0.57*</td>
<td>0.09</td>
<td>0.02</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Note.*  
* *p<.05; **p<.01
Chapter 7

Discussion
7.1 Discussion

7.1.1 Significance of Findings: Developmental Perspective

The results from this study show differences in neuropsychological and behavioral functioning in children whose mothers were exposed to organic solvents during pregnancy when compared with a matched group of children whose mothers were not exposed. Higher levels of maternal exposure, reports of detecting odor and experiencing symptoms of toxicity were associated with poorer neuropsychological and behavioral functioning in the children. Despite the fact that mothers in the exposed group reported high use of protective gear, a low level of symptoms associated with organic solvent toxicity, and low levels of detection of odor, the effects of exposure were still evident in their offspring. The exposed children scored significantly lower than the non-exposed children in areas of recall, language, memory, attention, manual dexterity, and behavior. In addition, all non-significant group differences were in the expected direction, with exposed children performing more poorly than non-exposed children.

Language functioning appeared to be affected commencing in early childhood in the form of poor auditory comprehension, and persisted into later childhood when other areas of language performance appeared to be affected. Specifically, the older children performed more poorly than their matched controls in subtests measuring word knowledge and fluency, integrative thinking, and memory. The sample size in the Toddler group was relatively small, which could account for the fact that only a few language measures showed significant differences. Alternatively, differences in functioning may be subtle and less apparent when the child is younger and may become more evident as development continues. Although the exposed children were not in the “clinical” range, even small deficits in functioning can place a child at risk for challenges in life and may limit these children in their potential for achievement in the areas discussed. These language challenges could be in the school setting
where skills take longer to learn or in social settings in which the child may face challenges interacting with others.

Maternal reports indicated that the exposed children in both the younger and older age groups displayed more behavioral problems than their non-exposed peers in the areas of anxiety and depression, destructive behavior, as well as symptoms associated with Attention Deficit Hyperactivity Disorder (ADHD). Behavioral functioning can impact a child in many aspects of life. Behavioral challenges may also become more evident or severe as the child moves into adolescence. Behavioral issues can pose challenges within the family setting, school environment, as well as social domains.

When the findings from this study are thought of in the context of a developmental perspective such as Bronfenbrenner’s framework (Bronfenbrenner, 2006) in which the child is viewed in the context of his or her environment from a multitude of levels, the influence of maternal exposure can be put into a larger context. According to Bronfenbrenner, the child is bi-directionally influenced by many levels including the: microsystem, the environment in which the child grows up, such as family, peers, school, as well as the child’s own biological factors such as gender; mesosystem, the relationships of those people / places within the child’s microsystem; exosystem, the effect on the child is indirect such as the parents’ work environment; macrosystem: which is the culture in which the child lives including cultural values; and the chronosystem, transitions that occur over a lifespan including divorce or other life events (Bronfenbrenner, 2006, Doran et al., 2005).

Any impairment of function can lead, through these multiple interactive environmental levels, to sub-optimal levels of performance and achievement in life. In our study we controlled, as much as possible, the child’s microsystem by using stringent matching criteria including: child’s age, maternal age, cigarette use, and socioeconomic status. In addition, we explored maternal IQ and education and, as expected, it was a significant predictor of child IQ. However, we were able to determine that exposure accounted for poorer performance in
the exposed children above and beyond maternal IQ. Further to this, the fact that mothers in both the exposed and non-exposed groups had the concern and the intellectual capacity to contact Motherisk about their respective exposures, speaks to the similarity of these two groups with the exception of the specific product to which they were exposed. The differences in functioning in the exposed children seen in the context of this complex interactive framework will lead to as yet undetermined potential outcomes, be they positive or more likely negative.

The child’s intellectual functioning may be influenced by a myriad of factors. For example, the impact that exposure to organic solvents may have on the developing brain in specific domains such as language functioning, may be attenuated when the child lives in a language-rich home and/or school environment (microsystem) but may be more evident if the child's environment was not buffered in that way. Similarly the impact of the mother’s exposure on her intellectual functioning or emotional well being might impact not only her child rearing skills but also her relationship with other members the family over time (the chronosystem). Prospectively following this cohort into later childhood and early adolescence to observe whether the differences in functioning between the two groups attenuate, persist, or become more significant as the child moves into a period of development that calls for higher levels of functioning, would be most valuable and interesting. For example, as the child moves into adolescence the differences observed in our cohort of children might become more or less evident which, in turn, might influence potential career options.

The cumulative risk literature suggests that there may be a linear relationship between the number of risk factors a child faces and child neuropsychological and behavioral functioning (Appleyard, K., Egeland, B., van Dulmen, M.H.M., & Sroufe, L.A., 2005; Rutter M, 1979; Sanson, A., Oberklaid, F., Pedlow, R., & Prior, M., 1991; Trentacosta CJ et al., 2008). Child functioning is not solely influenced by in utero exposure to organic solvents alone, but rather children are affected by many factors that may alter their course of development. Similar to genetic susceptibility, in utero exposure may be the factor that initially leaves these children
more vulnerable to a poorer trajectory of development than those children whose mothers were not exposed to organic solvents during pregnancy. For example, a child who had not been exposed to organic solvents during in utero development may have a better capacity to deal with risk factors such as poor family dynamics, interpersonal challenges etc, than an exposed child. This may be even more evident if we were to examine a cohort of mothers who were exposed to organic solvents during their pregnancy in third world countries where protective gear may be unavailable, exposure levels may be higher, knowledge about the danger associated with exposure may be lower, and the accessibility to medical guidance may be poor. The cohort examined in this study are representative of a rather privileged society where all of the above exposure factors are minimal. Moreover, we know that the exposure risk in our cohort was very low and thus might represent the most optimal outcome for children who were exposed during in utero development.

### 7.1.2 Consistency with Earlier Reports

The results from this study are consistent with those reported by Saddik et al. (Saddik et al., 2005) in which children who were employed to work with organic solvents were compared with children who were not exposed to organic solvents. Saddik et al. found significant differences specifically on the WISC-R Digit Span and the grooved pegboard, which are similar to the findings from this study of children who were exposed not during childhood but rather during in utero development.

The findings from this study are consistent with animal toxicity data as well as studies with young children (Till et al., 2001) which suggested differences between exposed and non-exposed offspring in language and graphomotor functioning, visual acuity, and color vision. Earlier research with young children (Eskenazi et al., 1988) demonstrated no significant differences between exposed and non-exposed children. There were a number of methodological limitations in this earlier study that we attempted to rectify in our study. We ensured exposure to organic solvents commenced in the first trimester when the important
phase of organogenesis begins. We included a broad age range to ensure we did not miss effects in young children that may have been compensated for by the brain’s plasticity if that same child were to be examined at an older age. We also wanted to see if there were latent effects not seen on examining younger children that would be manifest as the child gets older. We included a wide range of assessment measures that were able to detect subtle differences between the two groups. We were able to determine with more certainty that the findings from our study were a result of exposure and not a result of observer bias (by using examiners blind to the child’s exposure status), age of mother at time of child’s birth, or recall bias regarding aspects of exposure in mother’s. Moreover, this study shows, for the first time to our knowledge, that maternal intellectual functioning was not the strongest predictor of poorer outcome on domains that were significantly different between the exposed and non-exposed groups.

### 7.1.3 The Vulnerability of the Central Nervous System

The central nervous system consists of a large amount of lipids. Organic solvent are lipophilic and are able to cross the placenta, gain direct access to the fetal brain and potentially accumulate in the central nervous system in high concentration (Julvez & Grandjean, 2009, Johnson et al., 1987). In their review of the literature on neurodevelopmental toxicity risks associated with occupational exposure during pregnancy, Julvez et al (2009) discussed the fact that only five chemicals have been documented as causing neurodevelopmental toxicity. The documented chemicals include: arsenic, lead, methylmercury, toluene, and polychlorinated biphenyls (Julvez & Grandjean, 2009). As a result of our study and others reporting on the possible neuropsychological and behavioral effects associated in utero organic solvent exposure, toluene is now recognized as a neurodevelopmental toxin (Julvez & Grandjean, 2009).

In utero exposure to mercury, lead and nicotine are well known to cause neuropsychological and behavioral consequences in offspring (Bruin et al., 2010; Espy KA et al., 2011; Gressens
The historical course of labeling these chemicals as neurodevelopmental toxins is similar to that of organic solvents. For example, Grandjean, Satoh, Murata, and Eto (2010) review the time line in labeling methylmercury as a neurotoxin. In 1865 a report was released by Edwards, suggesting a pattern of symptoms that may have been associated with laboratory accidents involving mercury. The warning was largely ignored until many citizens of seashore towns along Japan’s coast (1950s and 60s) as well as Canadians living near Kenora, Ontario (1960s) either became ill or died from symptoms now recognized as mercury poisoning (D’Itri PA & D’Itri FM, 1978; Grandjean P et al, 2010; Social Scientific Study Group on Minamata Disease, 1999; Wheatley B, Barbeau A, & Clarkson TW, 1979). The first publication of neurodevelopmental toxicity of methylmercury in two infants was reported in 1952. In the 1980s scientists reported that due to the vulnerability of the developing brain, neurodevelopmental toxicity was evident at one-fifth of the dose that produced symptoms of neurotoxicity in adults (Marsh DO et al., 1987). The key point is that as a result of inconsistencies in the literature on prenatal vulnerability, an international agreement aimed at protecting the fetus against exposure to methylmercury during pregnancy was formed only in 2003 (Grandjean P et al., 2010). The effects of in utero exposure to methylmercury was determined to be dose-dependent, the higher the maternal dose, the more symptoms of neurotoxicity was evident in their offspring (McKeown-Eyssen GE, Ruedy J, & Neims A, 1983). The body of evidence associating in utero exposure to organic solvents has slowly been growing over the past one hundred years, similar to the trajectory seen with methylmercury as well as other well established neurotoxins.

The empirical data on the vulnerability of the human brain to teratogenic insult has grown immensely as noted above. The evidence speaks to the extreme caution that is warranted when forming conclusions as to safe exposure limits during pregnancy. This is of particular concern as the mother may experience little or no symptoms of exposure while her fetus is being exposed to levels teratogenic to neuropsychological and behavioral development. We found no significant differences in maternal IQ between the exposed and non-exposed
mothers suggesting a low level of neurotoxicity in the mothers. However, similar to methylmercury, the dose of exposure may not have produced neurotoxic effects in the mother (evidenced in similar functioning intellectually) but it was enough to produce effects in the offspring of exposed mothers. As noted earlier, neurodevelopmental toxicity from methylmercury was evident at one-fifth the dose that produced symptoms of neurotoxicity in adults, which may be similar to our findings with organic solvent exposure.

The literature suggests exposure to organic solvents in adults has been linked to cortical atrophy as well as focal abnormalities in the parieto-occipital area (Juntunen et al., 1980) and Till et al. (2005) also reported visual abnormalities in exposed offspring. Wernicke’s area in the left temporal lobe is the part of the brain that controls language comprehension and Broca’s area controls language production. Further studies are needed to determine if there was any difference in these areas of the cortex in exposed offspring.

The findings from this well controlled study support the hypothesis that exposure during in utero development affects neuropsychological and behavioral development as well as the hypothesis that increased exposure and reporting of symptoms associated with exposure toxicity further exacerbate the effects of exposure. Literature review coupled with findings from this study show that exposure to organic solvents across the lifespan from conception into adulthood is associated with a characteristic pattern of adverse including: areas of recall, attention, language, manual dexterity, as well as behavioral functioning (Saddik et al., 2003).

The current safety standards for exposure to organic solvents were designed for adult exposure. These standards and guidelines need to be reevaluated in light of the results from this study and other reports of associate risk of exposure during pregnancy. The potential for teratogenic consequences during the period of organogenesis exemplifies the susceptibility of the developing fetus. The following example highlights the extreme sensitivity of the developing fetus. The palate and lip form by fusion of tissues during the first six to eight weeks of pregnancy. Exposure to a teratogen during this critical period can result in a cleft
lip or palate. As a result of the rapid proliferation of cells, exposure to a teratogen during a one hour period can lead to a malformation. The same teratogenic exposure after this critical period may not lead to a malformation. This underscores the challenge of determining when and what dose constitutes a safe level of exposure. There may be no “safe” exposure limit for organic solvents during pregnancy. The fetal brain is vulnerable throughout pregnancy, precautionary measures should be applied in occupational settings to minimize exposure risk.

7.2 Strengths of the Study

This study was the first to prospectively investigate the cognitive and behavioral effects of exposure to organic solvents during in utero development while controlling for maternal influence. Including maternal intellectual functioning and education allowed these factors to be explored and quantified as to their influence on poorer performance. The investigator and psychometrists were all blind to the exposure status of the children, minimizing the chance for bias in test interpretation. The inclusion and exclusion criteria were stringent, which minimized potential confounding variables. The matching criteria were also very specific; for example the researchers used very tight guidelines for matching socioeconomic status, child’s age, and maternal age, maximizing similarity between the exposed and non-exposed children with the exception of exposure to organic solvents.

By including a broad age range (18 months – 8 years eleven months) we observed a pattern of exposure correlates from a developmental perspective. The assessment battery was comprehensive in its neurodevelopmental assessment scope, yielding scores in gross neurocognitive and behavioral functioning as well as subtest scores that revealed subtle but potentially important differences between the exposed and matched comparison groups. Previous studies did not ensure exposure commenced during the first trimester when the central nervous system begins to develop. By not controlling for maternal education and IQ
as well as not being blinded in previous studies, conclusions from this study have more weight by virtue of the study design.

The Motherisk facility provides an exceptional setting from which to embark on a study of this nature. There are few organizations that exist in which capturing this information would be possible or ethical. The researchers were able to obtain data during the mother’s pregnancy (at which time very little was known about the safety of exposure to organic solvents during pregnancy in humans) and prospectively follow these mothers as they progressed through pregnancy and well into their child’s development.

### 7.3 Limitations of the Study

Testing the effects of exposure to organic solvents during pregnancy is very challenging for several reasons: exposure is not typically to one single chemical, but rather a multitude of organic solvents simultaneously; there may be unknown byproducts involved; duration and timing of exposure is often unclear (first trimester only versus throughout pregnancy); and the specific amount of chemical actually absorbed may be unknown (i.e., being able to detect the smell of organic solvents is not necessarily indicative of a clinically significant exposure as the human olfactory system can detect a few parts per billion in numerous compounds).

The results from this study may be a conservative estimate of the potential negative effects of in utero exposure to organic solvents during pregnancy. The sample of women included in our exposed group may not be representative of the population of women who are occupationally exposed to organic solvents for several reasons including:

- The majority of the women who contacted Motherisk about exposure to organic solvents and were included in this study worked as laboratory technicians or in factories. However, we know that women who work as estheticians and hair stylists, for example, are also frequently exposed to organic solvents and were under-
represented in our sample. Typically, women in the beauty industry do not work in well ventilated areas and infrequently wear protective masks. Overall, a high proportion of the mothers in the exposed group of this study reported employing protective measures to minimize exposure risk and a relatively low number of symptoms associated with organic solvent exposure toxicity. Assessing women who are less aware of the potential effects of solvent exposure may yield more significant differences than those seen in this study.

• The women in this study included only those who were motivated to call a free teratogen information service. The mothers in both the exposed and non-exposed groups were interested enough in the safety of exposure (to organic solvents or other types of exposure) to contact Motherisk during their pregnancy. The women who called the Motherisk helpline may have had a greater awareness about the potential danger associated with chemical exposures and may have potentially protected themselves or their fetus more than other women who may not have been as conscientious or may have assumed that their work environment was safe. This factor in and of itself could mean that these children may already be in a more advantageous environment than those children whose mothers never called the Motherisk helpline.

• The women in the exposed group reported breastfeeding their children for significantly longer than their matched non-exposed cohort. Again, this might suggest that the exposed mothers were attempting to provide the most optimal trajectory of development for their children.

• The cohort that was included in this study may not be representative of other populations. The children in our study theoretically faced one risk factor (exposure) that might impact their neuropsychological and behavioral functioning. Women in more impoverished regions of the world might face additional risk factors such as low socioeconomic status, poor nutrition, and lower maternal education that may have cumulative adverse effects and potentially lead to more severe outcomes. Furthermore, in these settings protective gear might not be available, exposure levels might be higher, and information on safety might not be accessible.
7.4 Implications of Findings:

7.4.1 Safe Exposure Limits

The importance of this study lies in its ability to impact several levels of industry to bring change to existing standards with the aim of protecting the unborn fetus. The historical course in labeling chemicals as developmental neurotoxins is long and not without adverse clinical consequences often reported in the literature in small case reports or series. The aim of the following section is to discuss how governing bodies are attempting to implement changes toward protecting the developing fetus.

The American Conference of Governmental Industrial Hygienists (ACGH) Worldwide 2004 recommended that the additive or synergistic effects of exposure to many organic solvent compounds composed of a mixture of different solvents warrants a specific formula for calculation of safe limits during pregnancy (ACGIH Worldwide 2004). Although this is the recommendation, the specifics regarding calculations and exact solvent mixtures most toxic is missing from the OHS regulations. Thus, the likelihood of industry implementing these suggestions is very low.

In Canada guidelines regarding safe exposure limits for adults exist within regulatory bodies managed provincially, however the extent to which these guidelines are upheld is largely unknown. As women currently represent over one-third of the world’s economically active population and over 50% of women of working age are part of the labor force in North America, the possibility for exposure and subsequent neurodevelopmental consequences is significant. Strategies for minimizing risk include appropriate protective gear, ventilation, and consideration of changed work duties or relocation during pregnancy.

The fact that significant differences between the exposed and non-exposed groups were evident raises the issue of safe occupational levels as discussed by Schardein (2000). The
Safe level of exposure to any chemical is defined as no observable effect level (NOEL). Specifically, this refers to the concentration of chemicals that do not result in identifiable differences between exposed and non-exposed persons. Levels above NOEL are termed LOEL or lowest observable effect level. LOEL is the lowest dose above NOEL that produces an identifiable difference between exposed and non-exposed persons. In our study, the exposed mothers had no adverse effects that we could quantify and less than 1% (.81%) of these women reported any symptomatology of exposure whatsoever. Adverse effects were seen in the exposed group which highlights the fact that LOEL and NOEL levels in pregnant women are much lower than that currently recommended in the non-pregnant state. It bears repeating that there may be no “safe” level of exposure to organic solvents during pregnancy.

### 7.4.2 Information Dissemination

The course of identifying chemicals, such as methylmercury, as neurotoxic agents exemplifies the necessity for making international agreements to enforce change at every level where exposure may occur during pregnancy. The following is an overview of the information available on the teratogenic effects of organic solvents, how the public can use the information, followed by a brief review of current legislation aimed at protecting the fetus.

The number of resources in which to find information regarding human toxic exposures is vast and includes the following: Canadian Centre for Occupational Health and Safety, International Programme on Chemical Safety, Agency for Toxic Substances and Disease Registry, which is part of the Centre for Disease Control, the Environmental Protection Agency, and the Occupational Safety and Health Administration. These information resources are very helpful for data regarding adult human exposure; however, limited data are available on teratogenic exposure risks or limits. The state of California publishes one of the only lists geared at least to some extent to birth defects associated with chemical exposures (Proposition, 2003).
The development and publication of an international database of categorized chemical exposure limits, teratogenic risk and detailed risk assessment techniques would amass the literature that exists into a cohesive database that would simplify extrapolation of data from various resources into a centralized source in which data is obtained and maintained by a central governing body. A list of organic solvents for example might include the following information: specific organic solvent; category (i.e., aliphatic versus aromatic hydrocarbon); industry or environment in which exposure might occur; threshold level or LOEL; recommendations for minimizing exposure; teratogenic risk (structural, functional, metabolic, neurodevelopmental, and behavioral); as well as associated literature to support findings for each category.

The database might also include legislation that are currently in place as an example of how governing bodies might protect the pregnant woman and her unborn child. An example of this legislation from both Canada and the United States are briefly discussed in the following section and these could be used as models from which to develop better, or in many instances, the first guidelines designed specifically for pregnant women.

Information dissemination is an important variable and can be evidenced by using cigarette smoking as an example of how large scale education can change the course of exposure to a teratogen during pregnancy. Cigarette smoking is now widely accepted as a known teratogen and most pregnant women understand that it is recommended that they not smoke during pregnancy. However, years ago this was not common knowledge. Methylmercury is another example that is following this same level of recognition and acceptance.

The advantage of having a centralized source for this information would be the ease by which information could be disseminated. Clinically, physicians and other health care professionals can use the information from this study coupled with earlier research to warn women of childbearing age about the potential danger associated with exposure to organic
solvents during pregnancy. Armed with this information, women will be more educated and may consider the effects not only of organic solvent exposure, but exposure to other substances as well during pregnancy. Should prenatal exposure occur, the information from our study along with earlier work might aid in the early detection of these young children so that intervention may assist them toward achieving their optimal level of functioning at various intellectual levels.

### 7.4.3 Applying Study Findings to Industry: How Can We Promote Change?

Although some guidelines exist to safeguard pregnant women against exposure to potential teratogens, many employers and employees are unaware of the guidelines, the ceiling limit, short-term exposure limit, or 8-hour time weighted average limit. Although employers are required to comply with the occupational health and safety guidelines, according to provincial officials, few companies have the expertise or are unwilling to comply and monitoring is virtually impossible with the small ratio of occupational hygienists to industry. In situations where an employer may attempt to comply, the equipment required to properly monitor levels is expensive and not often employed. Using existing models as guidelines and improving upon them for more widespread future legislation would be beneficial. The following is a summary of legislation presently in existence across Canada as well as a description of benchmark legislation in the state of California.

#### 7.4.3.1 Examples of Legislation Specifically Aimed at Protecting the Unborn Child:

##### 7.4.3.1.2 Quebec:

In 1991 Quebec passed the Occupational Health and Safety Act to protect pregnant or breastfeeding workers (Plante & Malenfant, 1998). In 1998 Plante et al. (1998) reported that approximately 40% of women in Quebec were given preventive reassignment positions
during their pregnancy. The “precautionary leave” or preventative reassignment states that any pregnant woman who presents her employer with a medical certificate indicating that her work poses risk to herself or her unborn child has the right to be reassigned to duties that she can perform and pose no risk to herself or her fetus. The woman must make the initiative herself, contact her physician, explain the hazard to the physician, the physician must then determine if he / she feels the working conditions pose a risk to the pregnant woman and or her fetus. The physician must then consult with an occupational health physician from the public health network, who provides a medical and environmental consultation report determining whether or not the occupational setting poses a risk. The pregnant mother’s physician then provides a certificate confirming the risks and making suitable suggestions (Plante & Malenfant, 1998). The onus is then on the employer to provide a safe reassignment suitable for a healthy pregnancy. Should safe reassignment not be an option, the woman is able to stop working and the Quebec Occupational Health and Safety Commission (financed by contributions from all employers) will provide benefits at 90% of her net pay (Plante & Malenfant, 1998).

7.4.3.2 Benchmark Legislation in California:

The State of California has enacted the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition, 2003), known as Proposition 65, which was aimed at protecting California citizens and the State’s drinking water from chemicals that were known to cause cancer, birth defects or reproductive hazards. The Act requires that the Governor of California publish a list of chemicals at a minimum of once per year. The most recent list of chemicals was published September 2, 2011 and contains over eight hundred chemicals including solvents such as benzene, toluene, various glycols, and trichloroethylene (OEHHA, 2010). The cost associated with enforcing the Act was targeted at the offenders rather than the taxpayers. The act requires any individual who during the course of business exposes any other individual to one of the listed chemicals to present that individual with a “clear and reasonable warning” (Proposition, 2003). Any person, business, or industry found to violate the act may be
punished in a court of law in the amount “not to exceed two thousand five hundred dollars per day” for each violation. The state of California is considered to be at the forefront of environmental protection with laws such as the California emissions law and the Clean Air Act. California has set the standard in North America with these groundbreaking changes. Proposition 65 is a more recent development and may also serve as a benchmark for other states and countries around the world.

### 7.5 Future Directions

A potential pitfall of any epidemiologic study investigating reproductive risks associated with organic solvent exposure, is the likelihood that most women would be exposed to a multitude of chemicals simultaneously (i.e., laboratory technicians) rather than one specific organic solvent. However, there are physicochemical and toxicological similarities that make lumping of these compounds biologically plausible. In our series, women were exposed to numerous organic solvent compounds (refer to Table 7); larger studies will be needed to sort out which specific organic solvents pose a risk to pregnant women and their fetus. Methodologically, this situation may resemble the reproductive risks of environmental tobacco smoke, in which women are exposed to 1400 different toxins and the specific culprits have not yet been elucidated. However, with environmental tobacco smoke, these toxins are different chemically and toxicologically.

Future studies might focus on particular organic solvents by conducting research within a specified work environment such as dry cleaning or graphic design where the researchers could ascertain the type of chemical exposure as well as precise details about protective gear employed. Techniques of biological monitoring to elucidate the protective value of equipment utilized by pregnant women in these occupational settings would be beneficial. This would not only benefit the pregnant woman but also others working in occupational settings where exposure to organic solvents may occur.
The neurocognitive test battery employed in this study covered a large number of domains and was developmentally appropriate for the broad age range; however this resulted in a relatively small number of subjects for some of the outcome variables. A larger sample size in each of the age categories could alleviate this limitation. Limiting the scope of neurocognitive assessment based on the findings from this study to include areas of language functioning and specific behavioral domains could also yield higher sample size in each category. Prospectively following this cohort through to the next phase of life would be most interesting to see how this cohort performs intellectually and behaviorally over time.

7.6 Summary:

The fetal brain is vulnerable throughout pregnancy, every effort should be made to inform pregnant women of the potential risks of exposure to organic solvents. Further evaluation of the potential neurodevelopmental toxicity of organic solvent exposure is merited. Studies designed to clarify exposure effects in regard to specific solvents, dose levels, and timing of exposure will be most valuable. The results from this study may be a conservative estimate of the potential effects associated with in utero exposure to organic solvents. The sample of women in the exposed group took precautionary measures that may not be representative of other populations of exposed pregnant women. The findings reported would support minimizing maternal (and thus fetal) exposure to organic solvents during pregnancy until more definitive risk assessment is possible. Strategies for minimizing risk include appropriate protective gear, ventilation, and consideration of changed work duties or relocation during pregnancy. Current safety standards and guidelines were designed for adult exposure; these guidelines need to be reevaluated in light of the results from this study and other reports of associated risk of exposure during pregnancy. Conservatively, exposure to organic solvents should be completely avoided in pregnancy.
7.7 References


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Chapter 8

Exposure to Organic Solvents During Pregnancy:

Essential Review for the Health Care Provider

This chapter has been prepared as a stand-alone paper for publication and contains its own list of References.
8.1 Introduction

Organic solvents are one of the most prevalent sources of workplace chemical exposure reported by pregnant women (Bentur & Koren, 1991, McDiarmid & Gehle, 2006, NIOSH, 1987). The vulnerability of the developing fetus to environmental toxicants makes it essential for clinicians and physicians to consider the workplace environment of their patients during pregnancy to ensure the safety of the developing fetus (Perrin et al., 2007).

Organic solvents are carbon-based solvents (they contain carbon in their molecular structure) that are commonly employed to extract, dissolve or disperse substances without causing a chemical change to either the compound or the solvent itself (Garlantezec et al., 2009). Organic solvents are found in industrial settings, the home environment (cleaning products), contaminated drinking water, or in the air from nearby industry. The National Institute for Occupational Safety and Health (NIOSH) now certifies many organic solvents as carcinogens (e.g., benzene, carbon tetrachloride, trichloroethylene), reproductive hazards (e.g., 2-ethoxyethanol, toluene), and neurotoxins (e.g., n-hexane, tetrachloroethylene, toluene) (Garlantezec et al., 2009). Toluene and mixtures of solvents containing toluene and ethers, ketones and hexanes represent the most common type of organic solvent exposure (Nunes de Paiva & Pereira Bastos de Siqueira, 2005). The occupational health literature suggests that exposure to organic solvents in humans is most often characterized by exposure to a mixture of multiple solvents rather than one specific solvent (Kramer et al., 1999, Angerer & Kramer, 1997, NIOSH, 1987). Although each specific type of organic solvent is heterogeneous, the compounds are typically referred to as a group as they tend to possess common characteristics including their volatility, odor, vapor pressure capacity, solvency, and capacity of travelling through layers of the skin (Hartman, 1995, Curtis et al., 1986).

There are a number of important points to consider when counseling pregnant women who may be exposed to organic solvents. The aim of this paper is to provide: a) an overview of variables that may place individuals at higher risk for teratogenic effects associated with
exposure to organic solvents; b) tools that can be used when conducting a risk assessment; and c) strategies to minimize exposure hazards. Providing accurate information is of critical importance as there is a fine line between educating a mother on how she can best protect both herself and her unborn child, and instilling excessive fear, which could ultimately result in unnecessary elective abortion of the pregnancy (Koren & Nickel, 2011).

One of the most important changes in environmental risk assessment over the past decade has been the realization that exposure to organic solvents may result in epigenetic changes and DNA mutations (Baccarelli & Bollati, 2009). Epigenetics is the study of heritable alterations in gene expression or phenotype that occur without changes to the DNA sequence (Bollati & Baccarelli, 2010, Wolfe & Guschin, 2000, Kishi et al., 2008, Perera & Herbstman, 2011). These epigenetic processes may mediate the toxicity of chemical exposures (Baccarelli & Bollati, 2009). As a result of this discovery, chemicals are now also categorized according to their capability to cause epigenetic changes. This information has played an essential role in establishing environmental risks and has affected regulatory efforts to minimize exposure (Baccarelli & Bollati, 2009). The following sections provide a summary of the evidence of the vulnerability of the fetus to exposure as well as an overview of variables to consider in the risk assessment of pregnant women exposed to organic solvents.

8.2 Vulnerability of the Human Fetus

A teratogen is any agent, (i.e., medication, chemical, or herbal remedy) that has the capacity to interfere with the normal development of the fetus. A teratogen may cause abnormalities including physical malformations, metabolic or functional anomalies, intrauterine growth irregularities, neuropsychological impairments, or atypical behavior. Embryonal and fetal death can also result from exposure to a teratogen. Fetal exposure to teratogens may occur via maternal inhalation, oral ingestion, dermal touch, eye contact, or exposure to radiation (Dick, 2006). Adverse pregnancy outcomes such as spontaneous abortion, still-birth, small or large for gestational age, infant mortality, and morphological abnormalities (abnormalities in
the differentiation of cells and tissues that form the various organs and parts of the body) are clearly evidenced prenatally and at birth (Selevan et al., 2000) while abnormalities such as cancer, physiologic conditions, and neuropsychological deficits and atypical behavior may not be apparent until well into childhood or adulthood. In utero exposure to teratogens may also be linked to cardiovascular disease and degenerative neurologic abnormalities that occur later in life (Hu et al., 1997, Selevan et al., 2000, Drews et al., 1996, van Duijn et al., 1994, Needleman et al., 1990, Wadsworth & Kuh, 1997).

The impact that an exposure to a teratogen may have on the fetus is dependent on a myriad of factors, including the timing of exposure, dose, duration, and genetic variables for both the mother and the fetus, as detailed below. Despite the fact that many complicated processes are happening throughout embryonic development, the likelihood of a malformation developing is relatively small. Congenital malformations occur in 1-3% of births in the general population, however, follow-up later in life suggests that this number may rise to approximately 5%. In the group of infants with major malformations, it is estimated that 20-25% of the defects are of genetic origin, 65% are of unknown origin, 2-3% are likely a result of exposure to medications during pregnancy, and the remaining 7-13% of major malformations are thought to be associated with environmental factors including maternal disease, infection, mechanical problems, radiation, or chemicals (Nava-Ocampo & Koren, 2007, Schardein, 2000, Koren et al., 1998). Major birth defects are estimated to account for 20% of infant mortality (O'Rahilly & Müller, 2001).

8.3 Timing and Dose of Chemical Exposure

The primary organs in the developing fetus are formed during the embryonic period, from 18 to 60 days following conception (Koren, 2011). This period of development, termed organogenesis, is an extremely sensitive phase of intrauterine growth. Approximately half of all pregnancies are unplanned and many women are unaware that they have conceived during this early period of fetal development (Koren, 2011, Han et al., 2005). Exposure to a
teratogen during this sensitive period can result in a malformation. Emerging or newly formed organ systems in the fetus are at such an early stage of development that the enzymatic processes that either aid in protection against toxic substances or repair the damage caused by these substances are insufficient or absent (Garlanterezec et al., 2009). At the completion of organogenesis, only minor morphological or physiological defects may occur.

Shortly after conception the fetal brain begins to develop. Throughout the remainder of the pregnancy and well into early childhood, the human brain and central nervous system (CNS) continue to develop. Unlike all other body organs, this extended period of growth leaves the fetal brain vulnerable for the duration of pregnancy (Koren, 2011). Neuropsychological impairments following teratogenic exposure can range from no effect or subtle (within normal limits but lower functioning than a matched comparison group) to very severe, affecting many areas of functioning. Neuropsychological impairments might become evident during the first few years of life or may not become apparent until childhood and young adolescence when the individual requires skills for higher functioning (Rees et al., 2011).

Making a direct link between the etiology of a malformation, physiologic abnormality or neurodevelopmental delay and exposure to drugs or chemicals during pregnancy is challenging. Effects of in utero exposure to a teratogen may be evidenced by specific malformations that can sometimes be definitively linked to narrow periods of development (Polifka & Friedman, 2002). However, adverse effects of prenatal exposure may not be apparent at birth but may become evident at any period throughout the lifespan.

The dose of a teratogenic agent can affect the type and frequency of a malformation or neuropsychological deficit (McMartin & Koren, 1999, Wells, 1998). As an example: one milligram of thalidomide, ingested at any point during pregnancy, carries no risk of congenital malformation (Brent, 2004). In contrast, ingestion of fifty milligrams of thalidomide approximately three weeks after conception carries a significant risk of congenital malformation; however, this same dose of thalidomide taken in the second
trimester carries no risk of malformation (Brent, 2004; Nava-Ocampo & Koren, 2007). In a similar way, valproic acid has been shown to cause neurodevelopmental delay only at daily doses exceeding 1 gram (Koren et al., 2006). The timing of exposure to any agent is of equal importance to the teratogenicity of the agent itself.

8.4 Physical Malformations and Physiological Abnormalities Associated With In Utero Exposure to Organic Solvents

How solvents cause a malformation is very specific and highly dependent on the variables discussed earlier including dose, timing and duration of exposure. For example, when exposure occurs during the formation of limbs, the organic solvent might operate by causing focal necrosis in the apical area of the limb bud, which may stimulate a compensatory overproduction of phalangeal cells, resulting in polydactyly (six or more digits on the hand or foot) (Wells, 1998, McMartin & Koren, 1999).

The data on malformations associated with in utero exposure suggest a significant correlation between exposure to organic solvents and major malformations as well as poorer pregnancy outcome (McMartin et al., 1998, Stillerman et al., 2008). Table 21 outlines the existing evidence of teratogenic effects of exposure to organic solvents.
### Table 21

**Teratogenic Effects of Organic Solvents: Malformations and Pregnancy Outcome**

<table>
<thead>
<tr>
<th>Malformations</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS defects including: neural tube defects; hydrocephaly; anencephaly; meningomyelocele; hydranencephaly; meningocele; agenesis of corpus callosum; spina bifida</td>
<td>Desrosiers, et al., 2012; Aguilar-Gurdano, et al, 2010; Aschengrau, et al., 2009; Bentur &amp; Koren, 1991; Holmbery &amp; Nurminen, 1980; Holmberg, 1979</td>
</tr>
<tr>
<td>Oral clefts</td>
<td>Garlantezec, et al., 2009; Chevrier, et al., 2006; Cordier et al., 1997; Laumon et al, 1996; Arnold et al., 1994</td>
</tr>
<tr>
<td>Cardiovascular: left-sided obstructive heart defects (hypoplastic left heart); coarctation of the aorta</td>
<td>Loffredo, 2000; Cordier et al., 1997; Ferencz, et al, 1997; Tikkanen &amp; Heinonen, 1991; Tikkanen &amp; Heinonen, 1988</td>
</tr>
<tr>
<td>Fetal solvent syndrome, characterized by the following: growth deficiency; microcephaly; phenotypic anomalies including small midface, narrow bifrontal diameter, short palpebral fissures, deep-set eyes, low-set ears, micrognathia, blunted fingertips, small fingernails, and minor limb abnormalities, abnormal scalp hair patterning; thin upper lip; smooth philtrum; small nose, downturned mouth corners; large anterior fontanel; abnormal muscle tone; hemangiomata; renal anomalies; altered palmar creases</td>
<td>Bowen et al., 2005; Filley et al., 2004; Meggs, 2003; Costa et al.; 2002, Jones &amp; Balster, 1998; Arnold et al., 1994; Pearson, 1994; Hersh, 1985; Hersh et al, 1989; Goodwin et al., 1981</td>
</tr>
<tr>
<td>Esophageal stenosis</td>
<td>Garlantezec, et al., 2009; Wennborg et al., 2005</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>Lupo et al., 2012; Torfs et al., 1996</td>
</tr>
<tr>
<td>Genital Organs</td>
<td>Vaktskjold et al., 2011</td>
</tr>
<tr>
<td>Malformations</td>
<td>Authors</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Sacral agenesis</td>
<td>Kucera, 1968</td>
</tr>
<tr>
<td>Circulatory system</td>
<td>Vaktskjold et al., 2011</td>
</tr>
<tr>
<td>Gastrointestinal and Renal-urinary tract defects (hypospadias)</td>
<td>Garlantezec et al., 2009</td>
</tr>
<tr>
<td>Limb</td>
<td>Bianchi, et al., 1997</td>
</tr>
</tbody>
</table>

**Table 22**

*Pregnancy Outcome Following In Utero Exposure to Organic Solvents*

<table>
<thead>
<tr>
<th>Pregnancy Outcome</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion</td>
<td>Windham et al., 1991; Lindholm, 1995</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>Khattak et al., 1999</td>
</tr>
<tr>
<td>Shortened gestation</td>
<td>Wang et al., 2000</td>
</tr>
<tr>
<td>Infant small for gestational age / decreased birth weight</td>
<td>Chen et al., 2000; Ahmed &amp; Jaakkola, 2007; Sallmen, 2008</td>
</tr>
<tr>
<td>Impaired fertility</td>
<td>Sallmen, 2008</td>
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</table>
The central nervous system consists of a large amount of lipids. As organic solvents are lipophilic, they tend to accumulate in the central nervous system in high concentrations. The data on neurotoxic effects found in adults chronically exposed to organic solvents is extensive and include cortical atrophy, axonal and myelin sheath degeneration, abnormalities in the parieto-occipital areas, supranuclear palsy, disturbance of dopaminergic function, and cerebral blood flow abnormalities (Bockelmann et al., 2004, Jovanovi et al., 2004, Nilson et al., 2002, Vital et al., 2006). In the intrauterine environment, organic solvents are able to cross the placenta and gain direct access to the fetal brain (Julvez & Grandjean, 2009, Johnson et al., 1987, Laslo-Baker, 2012).

In a study of children born with central nervous system malformations, mothers of infants with malformations were four times more likely to have been exposed to one of 14 different organic solvents during their pregnancy than mothers of infants born with no central nervous system malformations (Holmberg & Nurminen, 1980). Of importance, most mothers of the infants born with central nervous system malformations were exposed to levels of organic solvents below the recommended occupational threshold limits (Holmberg & Nurminen, 1980). Maternal exposure to organic solvents was associated with vision abnormalities including reductions in contrast sensitivity and grating acuity as well as an increased risk of color vision impairment (Till et al., 2005).
8.5 Why Adverse Organic Solvent Exposure Might Affect One Fetus and Not Another: The Gene-Environment Interaction

With the significant advances in genomics research, there is a better understanding of the genetic root of many diseases (Kishi et al., 2008). Nawrot and Adcock (2009) used the analogy of an orchestra to demonstrate the concept of epigenetics. In this analogy the information contained in an individual’s DNA can be thought of as the notes of an orchestral score and epigenetics can be thought of as the conductor who interprets and controls the dynamics of the symphonic performance (Nawrot & Adcock, 2009, Perera & Herbstman, 2011).

Epigenetic effects can occur at any point from conception to death, however, the period of highest vulnerability is thought to occur during embryogenesis when rapid cell division and epigenetic remodeling is taking place (Perera & Herbstman, 2011, Foley et al., 2009). These changes in gene expression may not only have lifelong implications for the health of the exposed fetus, but may result in trans-generational effects as well (Perera & Herbstman, 2011).

Epigenetic regulation refers to the way in which the genome (all the hereditary information) integrates intrinsic and environmental signals (Jaenisch & Bird, 2003). Epigenetic regulation plays an important role in maintaining stability and integrity in the expression profiles of different cell types (Reamon-Buettner & Borlak, 2007). Under exogenous influence, there are at least several types of epigenetic processes that may occur including DNA methylation and alterations to chromatin proteins and RNA-associated pathways (Bollati & Baccarelli, 2010, Reamon-Buettner & Borlak, 2007). When epigenetic processes are misdirected, the resulting alterations in the development and differentiation of cells can lead to malformations (Reamon-Buettner & Borlak, 2007).
In a review of the literature, Perera and Herbstman (2011), of the Columbia Center for Children’s Environmental Health, discussed the implications that prenatal environmental chemical exposure can have for subsequent developmental disorders and disease that may present in childhood over the lifetime or transgenerationally (2011). Perera and Herbstman suggest that epigenetic markers can be used to aid in establishing the association between toxic environmental exposures and neurodevelopmental outcomes; however, they caution that more data are needed on individual susceptibility to epigenetic changes before these markers are used in risk assessment (Perera & Herbstman, 2011).

Viewing the gene-environment interaction in a multifaceted framework gives a broad overview of the many possible etiologies of pathologic outcomes (Lawler et al., 2004). The forces that can influence the course of fetal development include the physical, biological, and chemical environment that the pregnant woman is exposed to as well as the environment within the mother’s body. These factors in combination with genetic variables synergistically affect how the fetus will develop (Wlodarczyk et al., 2011). There are myriad genetic mutations or variants within each individual and these unique genetic features play a role in determining why an identical teratogenic exposure results in a serious malformation in one fetus and no malformation in another (Wlodarczyk et al., 2011).

Lawson et al. (2006, 2003) defined two categories for grouping individuals according to their vulnerability to environmental toxins: those who possess a particular allele that places them at elevated risk for disease or birth defects irrespective of other influences such as environmental exposures; and those with what are termed susceptibility genes, which increase the risk of disease or birth defects dependent on the interaction of genetics and environmental exposures. This area of occupational reproductive health research is moving toward identifying teratogens that have a similar mode of action based on a specific pattern of gene expression (Lawson et al., 2006). Lawson et al. (2006) noted that since gene expression aberrations exist prior to the timing of reproductive exposure, risk assessment might involve gene expression data as a form of primary intervention.
Animal studies suggest that exposure to organic solvents such as trichloroethylene result in decreased methylation of genes and increased levels of mRNAs and proteins (Tao et al., 1999, Baccarelli & Bollati, 2009). Human studies suggest that low-level exposure to benzene among gasoline station attendants and traffic police officers is associated with changes to DNA methylation (Bollati & Baccarelli, 2010, Baccarelli & Bollati, 2009). Specific maternal and infant genotypes can modify the effect of organic solvent exposure, for example, in some genotypes causing a shortened gestational period while in others the same organic solvent exposure has no effect on the gestational period. This specific interaction with organic solvent exposure was seen even at low levels of exposure (Qin et al., 2008). Wang et al. (2000) reported that low-level occupational exposure to benzene associated with two susceptibility genes resulted in decreased length of gestation, suggesting a gene-environment interaction.

### 8.6 Genetic Influence on Brain Plasticity

Brain plasticity refers to the ability of the developing brain to reorganize as a result of environmental stimuli (Missitzi et al., 2011). Brain plasticity can be described at the cellular level as changes in synaptic function in terms of their strength and number, or as changes in neural networks and reorganization of representational maps or centers of control (Pearson-Fuhrhop & Cramer, 2010). As a result of this plasticity, compensation for insult during fetal development can result in little or no detectable neuropsychological or behavioral effects later in development (Richardson et al., 1998). Missitzi et al. (2011) assessed the genetic variation of brain plasticity in monozygotic and dizygotic twins. To examine plasticity, the authors used paired associative stimulation to the median nerve and pollicis brevis muscle. The changes in the motor evoked potentials in the muscle triggered by the stimulation are thought to result from strengthening synapses connecting neurons. Corticospinal excitability was measured 30 minutes after the intervention. Missitzi et al. (2011) reported that intrapair differences were almost double for dizygotic twins when compared with monozygotic twins.
The findings from this study suggest that genetic variables significantly contribute to differences in brain plasticity between individuals. If these findings are applied to in utero insult, they might suggest that the ultimate effect of organic solvent exposure on any individual fetus might be at least partially determined by the genetic capacity to compensate for the insult.

The area of epigenetic research is in its infancy with respect to its application to maternal-fetal toxicology, but it provides hope that as research progresses in this area, clinicians may be able to identify individuals who are more vulnerable to particular types of chemical exposures.

8.7 Safe Exposure Limits During Pregnancy May Be Lower Than Those Established for Adults

The definition of threshold dose is that amount of any substance below which the risk of death, structural malformation, intrauterine growth retardation, or functional deficit of either a physiologic or neurocognitive nature is not significantly greater than that observed in individuals who have not been exposed (Brent, 2004). The dose-response threshold below which no observable effects are seen following exposure has been defined for many agents in both the human adult and the animal teratology literature. An important point to emphasize is that these threshold limits have been shown to be different in human pregnancy in terms of their teratogenic dose-response curves (Laslo-Baker, 2012).

The data on the safety of exposure during pregnancy are limited and exposure limits are often established based on information from non-pregnant adult studies. The literature suggests that generalizing these limits to pregnancy can be inaccurate (Laslo-Baker, 2012). In a study conducted by Laslo-Baker et al. (Laslo-Baker, 2012, Laslo-Baker et al., 2004), it was found that children whose mothers were exposed to organic solvents during pregnancy displayed a
lower level of functioning when compared with their matched peers (not exposed to organic solvents or any known teratogen in utero) on tasks in cognitive, language, motor, and behavioral domains. Although the scores on measures of behavioral functioning were not in the abnormal range, the mothers of exposed children reported more behavioral problems. In utero exposure to organic solvents predicted lower scores on global measures of verbal IQ, receptive and expressive language scales above and beyond the effect of maternal intellectual functioning. Higher levels of exposure (detecting odor, longer duration, and a higher total number of toxicity symptoms) were associated with poorer outcomes on behavioral and motor function tests. Despite the fact that the exposed mothers experienced minimal symptoms of toxicity, detrimental effects were still evident in their offspring. This suggests that chemical exposure limits considered to be acceptable for adults may not be safe for the developing fetus. Therefore, these dose-response threshold limits may need to be reevaluated or redefined in occupations where pregnant women might be exposed (Laslo-Baker, 2012).

Grandjean & Landrigan (2006) and Julvez & Grandjean (2009) reviewed the literature on neurodevelopmental toxicity risks associated with occupational exposure during pregnancy. The authors noted that over two hundred industrial chemicals have been formally documented as neurotoxins in the adult literature, however only five chemicals have been documented as neurodevelopmental toxins (Grandjean & Landrigan, 2006; Julvez & Grandjean, 2009). The documented chemicals associated with neurodevelopmental toxicity are: arsenic, lead, methylmercury, organic solvents, and polychlorinated biphenyls (Julvez & Grandjean, 2009). Although organic solvents are one of the few industrial chemicals currently documented as neurodevelopmental toxins, it is suspected that this current list of chemicals is incomplete and highlights the fact that there is a paucity of research in this area as a whole.

Neurodevelopmental toxicity from methylmercury was evident at one-fifth the dose that produced symptoms of neurotoxicity in adults (McKeown-Eyssen et al., 1983). As in the case of methylmercury, the dose of exposure to organic solvents may not produce neurotoxic
effects in the mother (evidenced by a lack of change in cognitive function) but may be enough to produce effects in the offspring of exposed mothers.

### 8.8 Minimizing Exposure Risk

The optimal approach to minimizing exposure risk to organic solvents would be to remove the pregnant mother entirely from the environment in which exposure might occur. As this is not always possible, there are measures that can be employed to reduce exposure to organic solvents, such as: using appropriate protective gear; ensuring that proper ventilation is in place; making a change in work duties; or relocating the worker during pregnancy.

The safe level of exposure to any chemical is defined as the no observable adverse effect level (NOAEL) (Schardein, 2000). Specifically, this refers to the concentration of chemicals that do not result in identifiable differences between exposed and non-exposed persons. The lowest observable adverse effect level (LOAEL) is the lowest dose above NOAEL that produces an identifiable difference between exposed and non-exposed persons (Schardein, 2000). The 8-hour time weighted average limit is the concentration of a substance in air which may not be exceeded over an 8-hour work period (WorkSafe, 2003).

Although some guidelines exist to safeguard pregnant women against exposure to potential teratogens, many employers and employees are unaware of these limits or of the changes that may be needed with respect to these levels during pregnancy (Laslo-Baker, 2012). Employers are required to comply with occupational health and safety guidelines. However, according to Canadian data, many companies do not have the expertise or are unwilling to comply, and monitoring is virtually impossible given the small ratio of occupational hygienists to industry. Even when an employer attempts to comply, this might be impossible given the cost of the equipment required to properly monitor levels and the skill required to use it (Laslo-Baker, 2012).
Table 22 outlines several strategies to minimize exposure to organic solvents during pregnancy that should be considered.

**Table 22**

*Strategies to Minimize Exposure Risk During Pregnancy*

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relocate worker.</td>
<td></td>
</tr>
<tr>
<td>Monitor exposure.</td>
<td></td>
</tr>
<tr>
<td>Use recommended personal protective equipment specific for the organic solvent or mixture of organic solvents (keep solvents off skin and clothing).</td>
<td></td>
</tr>
<tr>
<td>Ensure eyes are properly protected.</td>
<td></td>
</tr>
<tr>
<td>Remove clothing immediately should it become soiled or dampened by an organic solvent.</td>
<td></td>
</tr>
<tr>
<td>Replace gloves as recommended by the manufacturer to maintain proper protective action (breakthrough time, degradation, penetration, and permeation are important variables to consider when assessing effectiveness of gloves).</td>
<td></td>
</tr>
<tr>
<td>Ensure proper ventilation (ventilation and proper respirators should be used together rather than one or the other alone).</td>
<td></td>
</tr>
<tr>
<td>Educate employers.</td>
<td></td>
</tr>
<tr>
<td>Educate employees.</td>
<td></td>
</tr>
<tr>
<td>Use medical monitoring (using biological monitoring techniques such as mass spectrometry).</td>
<td></td>
</tr>
<tr>
<td>Ensure pregnant women do not wash hands with cleansers that contain organic solvents.</td>
<td></td>
</tr>
<tr>
<td>Cover or seal organic solvents when not in use (including soiled rags).</td>
<td></td>
</tr>
<tr>
<td>Label all containers containing organic solvents. Never store organic solvents in drinking cups, cans, or bottles.</td>
<td></td>
</tr>
<tr>
<td>Test respirators and all other equipment to confirm it is working properly (some respirators are ineffective for specific organic solvents).</td>
<td></td>
</tr>
</tbody>
</table>
Change respirator cartridges as per manufacturer’s recommendations (filter cartridges are not safe for use with all solvents, i.e., benzene).

Do not rely on detection of odor or maternal symptoms associated with organic solvent exposure toxicity.

Consult with an occupational hygienist or engineer when designing a work environment in which exposure may occur.

Maintain all equipment properly.

(Administration, 2007, Katz et al., 1997)

8.9 Risk Assessment of Occupational Exposure to Organic Solvents Prior to or During Pregnancy

The optimal time for counseling is prior to pregnancy when action can be taken to minimize exposure risk should the mother wish to proceed with planning a pregnancy. However, counseling is more often requested when exposure is current or has recently occurred (Testud et al., 2010). In discussion with the patient, it is important to note from the outset that a malformation can result from unknown etiology with or without exposure to any teratogen. The patient should also be informed that exposure to a teratogen does not necessarily mean that a major malformation or neuropsychological deficit will ensue (Nava-Ocampo & Koren, 2007).

The assessment process is a critical component in understanding the pregnant woman’s overall risk. This assessment is similar to that of any patient with a medical concern but requires additional information. The practitioner must take into account the woman’s current health status as well as her risk based on an empirical review of data specific to the type of chemical, dose, timing, and duration of exposure (Brent, 2004). Table 23 outlines variables to
be used in an assessment when counseling women on exposure risk prior to or during pregnancy.

### Table 23

**Assessment Variables for Women Exposed to Organic Solvents Prior to or During Pregnancy**

<table>
<thead>
<tr>
<th>Variables to assess</th>
<th>Specific details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mother’s current health status</strong></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>Age at conception, gravidity, parity, previous miscarriages</td>
</tr>
<tr>
<td>Pregnancy details</td>
<td>Is mother planning on becoming pregnant or currently pregnant? If currently pregnant, specify gestational details</td>
</tr>
<tr>
<td>Diseases complicating pregnancy</td>
<td></td>
</tr>
<tr>
<td>Exposures during pregnancy</td>
<td>Medications, vitamins, herbal preparations</td>
</tr>
<tr>
<td>Date of last ultrasound</td>
<td></td>
</tr>
<tr>
<td>Tests during pregnancy</td>
<td>Triple screen, amniocentesis, chorionic villus sampling (CVS), etc.</td>
</tr>
<tr>
<td>Other types of chemical exposure</td>
<td></td>
</tr>
<tr>
<td>Other teratogenic exposures</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>Location where exposure occurred</td>
<td>Home / factory / office</td>
</tr>
<tr>
<td>Dose of exposure</td>
<td>Can this be obtained from the employer?</td>
</tr>
<tr>
<td>Duration of exposure</td>
<td>How many days per week / hours / minutes per day?</td>
</tr>
<tr>
<td>Specific type of organic solvent involved</td>
<td>For example: toluene versus benzene</td>
</tr>
<tr>
<td>Route of exposure</td>
<td>Inhalation, dermal touch, oral ingestion, eye exposure, or multiple routes</td>
</tr>
<tr>
<td>Variables to assess</td>
<td>Specific details</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
</tr>
<tr>
<td>Current work status</td>
<td>Full-time / part-time / not working</td>
</tr>
<tr>
<td>Protective gear used?</td>
<td></td>
</tr>
<tr>
<td>Type of protective gear used</td>
<td>Gloves, respirator, mask (such as the N95 mask), fume hood</td>
</tr>
<tr>
<td>If gloves were used, was the material impermeable to organic solvents?</td>
<td></td>
</tr>
<tr>
<td>Ventilation in the exposure site</td>
<td>Type of ventilation? Is it in proper working order?</td>
</tr>
<tr>
<td>Are methods employed to test for level of exposure?</td>
<td>Biological monitoring / mass spectrometry</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, rash, headache, tremors, blurred vision, dizziness, drowsiness, or other side effects (should be differentiated from symptoms associated with the pregnancy itself)</td>
<td></td>
</tr>
<tr>
<td><strong>Side effects reported by colleagues</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Threshold limit for the organic solvent or group of organic solvents.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Possibility of job relocation or temporary reassignment</strong></td>
<td></td>
</tr>
</tbody>
</table>

Motherisk Intake Form. The Motherisk Program, The Hospital For Sick Children

Nava-Ocampo and Koren (2007) suggest that the counseling process should be based on the woman's health status and prognosis in the context of an evidence-based balance of the overall risk and benefit to both the mother and her unborn baby. These authors also suggest that the counseling process and determination of the risk-benefit ratio often requires a multidisciplinary team (Nava-Ocampo & Koren, 2007). This will enable appropriate action to be taken if needed. The physician or health care team will also be able to make recommendations as to steps that can be taken to minimize the risk associated with exposure
to both the mother and her unborn child (Nava-Ocampo & Koren, 2007). With further developments in epigenetics, the assessment process may grow to include more areas of genetic counseling and testing.

8.10 Perceived Risk:
How to Counsel the Pregnant Women About Teratogenic Risk During Pregnancy

Counseling pregnant women about the teratogenic risk associated with exposure to any chemical or medication during pregnancy is a sensitive topic. The information available on the Internet and in the lay media is extensive and is often not evidence-based. When considering teratogenic risk associated with exposure to any agent (medication, chemical, or the like) it is important to understand each individual woman’s knowledge and her perceived risk. If there is any uncertainty about the risk associated with the exposure, the patient should be referred to a local antenatal counseling service (such as The Motherisk Program at the Hospital For Sick Children in Toronto, Canada).

The specific “safe” levels of exposure to most organic solvents during pregnancy have not yet been determined. Although the relative risk of having a child with a malformation or neuropsychological consequences may be higher for a woman who is exposed to organic solvents during pregnancy, the absolute risk still remains reasonably low. In counseling a pregnant mother, the goal should be to ensure that proper measures are put in place to protect the mother and her unborn child. The health care practitioner must also make sure that the mother is not unduly alarmed such that she might jeopardize either her career or the pregnancy itself.
8.11 Summary

Determining the specific etiology of any malformation can be challenging if not impossible. There are many factors that can influence whether or not a chemical will exert a teratogenic effect. These factors include the dose, timing, duration, type of chemical exposure, and the type of protective measures taken. The literature suggest that exposure to organic solvents have been associated with physical malformations, physiological abnormalities, poorer pregnancy outcome as well as potential neurodevelopmental toxicity.

The area of epigenetic study is providing a rapidly growing body of information on the effects of the gene-environment interaction. Epigenetic research holds promise that biologic markers may provide data on which individuals are at higher risk from the toxic effects of organic solvent exposure. However, as yet there are no published studies specifically looking at the epigenetic or transgenerational effects of in utero exposure to organic solvents during pregnancy.

The threshold dose for exposure to organic solvents may be lower for the developing fetus during pregnancy than the adult who is exposed to the same amount. Measures can be taken to minimize exposure risk during pregnancy including: job relocation; proper personal protective equipment; ensure proper ventilation is in place; educate both the employers and the employee on safety of exposure during pregnancy; test equipment to ensure it is working properly; and optimally obtain proper consultation from experts in the field of maternal-fetal toxicology. The optimal time for risk counseling is prior to pregnancy, however minimizing exposure to organic solvents should be the goal at anytime during pregnancy.
8.12 References


Chapter 9

Pregnant Women Working With Organic Solvents:

The Gap Between Policy and Practice

This chapter has been prepared as a stand-alone paper for publication and contains its own list of References.
9.1 Occupational Exposure to Chemicals During Pregnancy

Over the past century awareness about the possible deleterious effects that exposure to toxins can cause in human beings has grown exponentially. Significant measures are now in place to help protect individuals from exposure to toxins in the occupational environment. Although awareness and knowledge about exposure risk have increased for many chemicals with respect to adult exposure risk, the knowledge and empirical data on safety of exposure to the unborn child during pregnancy has been limited.

Women currently represent nearly half of the workforce in Canada, the United States, and Europe (Ferrao & Williams, 2011, Cook & Lott, 2011, Spidla, 2010). In Canada 8.1 million and in the United States 72 million women were employed outside the home in 2009 and 2010 respectively. A significant proportion of women in the workforce are of childbearing age and many of these women are employed during their pregnancy. Bentur and Koren (1991) suggested that approximately 17% of women who worked during their pregnancy were exposed to teratogens (chemical or physical agents that can cause malformations or functional abnormalities in the developing fetus) during their pregnancy. Globally, women represent over one-third of the world’s economically active population and the possibility for exposure and subsequent neurodevelopmental consequences is significant.

One of the most common types of chemical exposures in adults are the class of chemicals termed organic solvents. These chemicals are used to extract or dissolve other chemicals. Examples of industries in which women are most likely to be exposed include: dry cleaning, printing, painting, manufacturing, clothing and textile, laboratory services, beauty salons, carpentry, and gasoline fuel attendant.
As part of my Ph.D. studies, I conducted a matched cohort study (Laslo-Baker et al., 2004) comparing the neurobehavioral functioning of children whose mothers were exposed to organic solvents in their occupational setting with a matched comparison group of children whose mothers were not exposed to organic solvents in their occupational setting. The findings suggested that children whose mothers were exposed to organic solvents during pregnancy displayed lower levels of functioning in selective cognitive, language, motor, and behavioral domains when compared to matched peers with no history of exposure. In utero exposure to organic solvents predicted lower scores on global measures of verbal IQ as well as on receptive and expressive language scales even when controlling for maternal intellectual functioning and education. These findings support the hypothesis that in utero exposure to organic solvents affects verbal performance independent of genetic or education factors. Factors associated with higher levels of exposure (detecting odor, longer duration and total number of toxicity symptoms) were also associated with poorer outcomes on behavioral and motor tests. Despite the fact that the exposed mothers experienced minimal symptoms of toxicity themselves, detrimental effects were still evident in their offspring (Laslo-Baker et al., 2004).

These findings are consistent with other research suggesting detrimental effects of in utero exposure to organic solvents (Till et al., 2001, Till et al., 2003, Till et al., 2005). Together, the results of these studies have significant implications given that millions of women of reproductive age around the globe are occupationally exposed to organic solvents on a regular basis.

The objective of the present report is to inform and educate those at all levels of industry from the governing bodies through the individual employer and employee on the risks/safety of gestational exposure to organic solvents. In Canada, gestational guidelines exist within provincial regulatory bodies, however the extent to which these guidelines are adhered to is largely unknown. Current safety standards and guidelines were designed for non pregnant
adult exposure, and hence they need to be reevaluated in light of the new findings from our work and other reports of associated risk of exposure during pregnancy.

These recent findings have helped increase awareness to occupational risks associated with exposure to organic solvents during pregnancy as evidenced by the reports in the literature suggesting that precautions need to be put in place to protect the pregnant worker (Duray & Mekow, 2011, Alex, 2011, OPSEU, 2004, Ginsburg et al., 2006, Kalkbrenner et al., 2010, Julvez & Grandjean, 2009, Windham et al., 2006, Howe, Schettler, 2008). In their submission to the Ontario Ministry of Labour, the Ontario Public Service Employees Union (OPSEU) discussed the results from Laslo-Baker et al. (Laslo-Baker et al., 2004) in the context of planned changes recommended to the Ministry toward protecting pregnant women. Alex (2011) referenced this study with recommendations to nurses and suggestions for barrier use and strategies to reduce exposure risks. Duray and Mekow (2011) also made recommendations partly based on the Laslo-Baker et al. (2004) findings for students in the gross anatomy laboratory.

Important in establishing policy and guidelines in industrial and regulatory bodies is the issue of safe level of exposure as discussed by Schardein (2000). The safe level of exposure to any chemical is partially defined by the no observable adverse effect level (NOAEL), which refers to the concentration of chemicals that do not result in identifiable risks as compared to the unexposed general population. Levels above NOAEL start with the lowest observable adverse effect level (LOAEL). LOAEL is the lowest dose above NOAEL that produces an identifiable difference from a normal or matched cohort. As many of the pregnant women in the Laslo-Baker et al. study (Laslo-Baker et al., 2004) study took steps to protect themselves, the NOAEL might be lower than that which is typically considered acceptable for an adult.

Methods such as biological monitoring are important clinical and research tools that are gaining popularity in the occupational health industry. Biological monitoring enables measurement of the internal dose of exposure within the human body and the type of
chemical exposure (i.e., toluene versus benzene exposure). The markers correspond to the unchanged organic solvent evidenced in blood analysis, metabolites of the organic solvent excreted in urine, serum bile acids, measurement of unchanged organic solvent in alveolar air, or mass spectrometry (Kramer et al., 1999, Angerer & Kramer, 1997, Nadeau et al., 2006, Nunes de Paiva & Pereira Bastos de Siqueira, 2005, Scheepers & Heussen, 2005). Mass spectrometry is an instrument that has the capability of identifying and quantifying chemicals in a substance. Biological measuring of exposure could be used to determine whether the protective gear and apparatus used in industry are safely protecting individual workers and specifically pregnant women (Laslo-Baker et al., 2004).

9.2 Applying Study Findings to Industry: How Can We Promote Change?

As funding to ensure that guidelines are upheld is typically sparse, there are several strategies that might increase compliance, such as education and penalization for noncompliance (Teo, 2012). Educating employers and employees on alternatives within the work environment, such as a change of work type or location, may alleviate the problem. Biological monitoring using techniques such as mass spectrometry could be enforced to routinely monitor the work environment. This would not only benefit the pregnant woman but also others working in occupational settings where exposure to organic solvents may occur.

In 2004, the American Conference of Governmental Industrial Hygienists (ACGH) recommended that the additive or synergistic effects of exposure to many organic solvent compounds composed of a mixture of different solvents warrants a specific formula for calculation of safe limits during pregnancy (ACGIH Worldwide 2004). Although the recommendation is clear, the specifics regarding calculations and exact solvent mixtures
which are most toxic is missing from the Occupational Health and Safety laws. Thus, the likelihood of industry implementing these suggestions is very low.

Although some guidelines exist to safeguard pregnant women against exposure to potential teratogens, many employers and employees are unaware of them, including the ceiling limit, short-term exposure limit, or the 8-hour time weighted average (TWA) limit (which is the concentration of a substance in air which may not be exceeded over an eight hour work period) (WorkSafe BC, 2012). Using existing models as guidelines and improving upon them for more widespread future legislation would be beneficial. At present, each province have their own specific guidelines for the Occupational Health and Safety Regulations and each province is mandated to enforce their own guidelines. The following is a overview of legislation that exists in three provinces within Canada as well as a summary of legislation description of benchmark legislation in the state of California.

9.3 Legislation Specifically Aimed at Protecting the Unborn Child: British Columbia, Ontario, Quebec and California

9.3.1 British Columbia

The current guidelines in British Columbia are outlined in the Occupational Health and Safety Regulations, which are enforced by WorkSafe BC (a government funded agency). The following is an excerpt from the Occupational Health and Safety Regulations (OHS, 2003), this section specifically refers to pregnant women:

*Part 5 Chemical and Biological Substances: Controlling Exposure*

*5.48 Exposure limits*
Except as otherwise determined by the Board, the employer must ensure that no worker is exposed to a substance that exceeds the ceiling limit, short-term exposure limit, or 8-hour TWA limit prescribed by ACGIH (American Conference of Governmental Industrial Hygienists).

5.58 Protective policy

(1) At any worksite where a worker is exposed to a substance which is identified in section 5.57(1) as having a reproductive critical effect, a sensitization critical effect or SEN notation, the employer must develop policy and procedures appropriate to the risk, which may include protective reassignment.

(2) The policy and procedures required by subsection (1) must

(a) Inform workers about the reproductive toxin and identify ways to minimize exposure to the toxin for a worker who has advised the employer of pregnancy or intent to conceive a child, and

(b) Identify ways to eliminate or minimize exposure to a sensitizer for a worker who is or may be sensitized to that substance. [Amended by B.C. Reg. 258/2008, effective January 1, 2009.]

Many employers and employees are unaware of the guidelines, the ceiling limit, short-term exposure limit, or 8-hour TWA limit. Although employers are required to comply with the Occupational Health and Safety laws, according to WorkSafe BC, few companies have the expertise or willingness to comply and monitoring is virtually impossible with the small ratio of Occupational Hygienists to industry. In situations where an employer may attempt to comply, the equipment required to properly monitor levels of exposure to the employee by the employer is expensive and not often available for the employee’s protection (WorkSafe BC, 2012). Currently the implementation of the guidelines is not being monitored and there are no defined penalties for non-compliance in British Columbia.
9.3.2 Ontario

The Ontario Ministry of Labour (MOL) is mandated to communicate and enforce the standards set forth by the Occupational Health and Safety Act (OHSA) as well as Regulations to protect the health and safety of workers (Dean et al., 2010).

The employer must provide information, instruction and supervision to a worker to protect the health and safety of the worker under clause 25(2)(a). The employer must acquaint the worker or a person in authority over a worker with any hazard in the work and in the handling, storage, use, disposal and transport of any article, device, equipment or a biological, chemical or physical agent under clause 25(2)(d), this may include the potential hazard of exposure to organic solvents in the workplace. The employer must also take every precaution reasonable in the circumstances for the protection of a worker under clause 25(2)(h) and this may include written policies and procedures on pumping gasoline, and provision of appropriate personal protective equipment if required.

The Ministry sends representatives to assess safety and compliance with regulations. Various actions can be taken if the business is found to be contravening the safety standards. These action include: immediate stop work orders; fines; or the employer may be given a list of items that must be implemented prior to a set date for reevaluation.

Under the Occupational Exposure Limits document with the Ontario Federation of Labour, mandatory substitution is recommended to discourage use of toxic substances in order to protect the health of pregnant workers rather than voluntary substitution in which the industry voluntarily removes toxic substances from the work environment.

The KPMG Canadian Environmental Management Survey of Canadian Corporate Executives found that 16% of corporations were motivated to take action when programs were under
voluntary rule, while 95% were motivated to take action when government regulations were mandatory (KPMG, 1994). Mandatory substitution guidelines would stimulate research into alternative, less toxic substitutes for organic solvents. These mandatory guidelines are not yet in effect.

9.3.3 Quebec

In 1991 Quebec passed the Occupational Health and Safety Act to protect pregnant or breastfeeding workers (Plante & Malenfant, 1998). Plante et al. (1998) reported that only approximately 40% of women in Quebec were given preventive reassignment positions during their pregnancy. The “precautionary leave” or preventative reassignment states that any pregnant woman who presents her employer with a medical certificate indicating that her work poses risk to herself or her unborn child has the right to be reassigned to a duties that she can perform and pose no risk to herself or her fetus. The woman must take the initiative herself, contact her physician, explain the hazard to the physician, and the physician must determine if he / she feels the working conditions pose a risk to the pregnant woman and or her fetus. The physician must then consult with an occupational health physician from the public health network, who provides a medical and environmental consultation report determining whether or not the occupational setting poses a risk. The pregnant mother’s physician then provides a certificate confirming the risks and making suitable suggestions (Plante & Malenfant, 1998). The onus is then on the employer to provide a safe reassignment suitable for a healthy pregnancy. Should safe reassignment not be an option, the woman is able to stop working and the Commission santé et de la sécurité du travail (CSST) will provide benefits at 90% of her gross salary (before deductions) until four weeks prior to the expected date of delivery or the end of her breastfeeding ** add Michel Gagne (Plante & Malenfant, 1998). This is by far the most advanced legislation in Canada, but the rate of compliance with it has not been studied thoroughly.
9.3.4 Benchmark Legislation in California

In response to growing concerns regarding the safety of exposure to chemicals, the citizens in the State of California voted on and approved an initiative in 1986 to address these concerns. This initiative lead to the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition, 2003), known as Proposition 65, which was aimed at protecting California citizens and the State’s drinking water from chemicals that were known to cause cancer, birth defects or reproductive hazards. The Act requires that the Governor of California publish a list of chemicals at a minimum of once per year. The most recent list of chemicals was published September 2, 2011 and contains over eight hundred chemicals including solvents such as benzene, toluene, various glycols, and trichloroethylene. Proposition 65 requires businesses to clearly state significant amounts of chemicals in products they purchase which can be used in either their homes or workplaces, or chemicals that are released into the environment (OEHHA, 2010).

The cost associated with enforcing the Act is targeted at the offenders rather than the taxpayers. The act requires any individual who during the course of business exposes any other individual to one of the listed chemicals to present that individual with a “clear and reasonable warning” (Proposition, 2003). Any person, business, or industry found to violate the act may be punished in a court of law to pay a sum not to exceed two thousand five hundred dollars a day for each violation (Proposition, 2003).

The state of California is considered to be at the forefront of environmental protection with laws such as the California emissions law and the Clean Air Act. California has set the standard in North America with these groundbreaking changes. Proposition 65 is a more recent development and may also serve as a benchmark for other states and countries around the world. Many states and provinces in Canada have legislation of varying degrees that are aimed at protecting pregnant workers, however, Proposition 65 is one of the first to mandate that the government publish a revised list of chemicals every year. The published list of
chemicals makes it much easier for the employer to look up chemicals to help determine the correct course of action.

In California, signs or posters can be seen throughout the State where exposure to toxic substances might occur. Unlike other states and provinces, the onus on determining the safety of exposure is placed on the employer, therefore encouraging a scientific analysis of each chemical that an individual may be exposed to in their occupational environment. Over the past several decades since its inception, many products have been reformulated and lists of less toxic chemical alternatives that can be used in occupational environments have been generated as a result of the Act (OEHHA, 2010). As noted earlier, mandated guidelines rather than voluntary guidelines with both legal and monetary consequences would likely have greater impact on the employer to ensure that the pregnant worker is properly protected.

9.4 Occupational Health Laws: Manitoba, Saskatchewan, Quebec, and Nova Scotia

The number of resources to find information regarding human toxic exposures is vast and includes the following: Canadian Centre for Occupational Health and Safety (CCOHS), International Programme on Chemical Safety (IPCS), Agency for Toxic Substances and Disease Registry (ATSDR) which is part of the Centre for Disease Control, the Environmental Protection Agency (EPA), and the Occupational Safety and Health Administration (OSHA). These information resources are very helpful for data regarding adult human exposure; however, limited data are available on teratogenic exposure risks or limits. Proposition 65 is one of the only published lists geared to some extent to birth defects associated with chemical exposures.

The development and publication of an international database of categorized chemical exposure limits, teratogenic risk and detailed risk assessment techniques would amass the
literature that exists into a cohesive database that would simplify extrapolation of data from various resources into a centralized source in which data is obtained and maintained by a central governing body. A list of organic solvents, for example, might include the following information: specific organic solvent; category (i.e., aliphatic versus aromatic hydrocarbon); industry or environment in which exposure might occur; threshold level or LOEL; recommendations for minimizing exposure; teratogenic risk (structural, functional, metabolic, neurodevelopmental, and behavioral); as well as associated literature to support findings for each category. The advantage of having a centralized source for this information would be the ease by which information could be disseminated. For example, information could be available to the pregnant mother; individual clinician; risk counselors; small businesses; larger industrial companies; provincial governments; and federal governing bodies.

Information dissemination is an important educational and preventative aspect for reducing risk of exposure as exemplified by the campaign to decrease the effects of cigarette smoking on pregnant women. Cigarette smoking is now widely accepted as a known teratogen and most pregnant women understand that it is recommended that they not smoke during pregnancy. However, years ago this was not common knowledge.

The necessity to protect the pregnant woman and her unborn child is critical. However, singling pregnant women for special protection becomes challenging when human rights laws are considered (Insider, 2012). Discriminating against workers is against the law when it is based only on gender. An employer must ensure that they comply with both the Occupational Health and Safety laws as well as human rights laws (Insider, 2012). The Occupational Health and Safety laws state that measures must be taken to protect workers from hazards and pregnant workers are protected under one or both of the following: hazard-specific provisions or the “general duty” clause.
In Manitoba and Quebec the Occupational Health and Safety laws generally state:

- A pregnant worker can refuse work that may pose a risk to her health or safety or that of her unborn child
- The employer may reassign a pregnant worker to another position that doesn’t pose such risks
- If the pregnant worker is reassigned, she retains all the benefits of her original, pre-reassignment position. (Insider, 2012)

All other provinces with the exception of Nova Scotia provide hazard-specific protections. The most comprehensive protection is in Saskatchewan where it states the following:

Section 308 of the Saskatchewan Occupational Health and Safety laws:
when a chemical or biological substance is present in the workplace in a form and to an extent that may be harmful to a pregnant worker, the employer must, as soon as reasonably possible after it becomes aware of the worker’s condition:

1. Take steps, when “reasonably practicable,” to minimize the worker’s exposure to the substance; or

2. At the worker’s request, assign her to less hazardous work, if such work is available. This only extends to what is reasonably practical. An employer is obligated to reassign to a position that is available to that employee, which is based on the woman’s seniority, qualifications, or contracted negotiations. There are no guidelines for situations where reassignment is not be available or practical.

To complicate matters further, an employer cannot treat a worker differently or make assumptions about her ability to work based solely on the fact that she is pregnant (Insider, 2012). Human rights laws require that the employer accommodates pregnant workers by
providing reasonable modifications to workplace policies, procedures and conditions so that the pregnant worker is able to continue working.

9.5 Are the Occupational Health and Safety Laws Being Implemented?

The Ministry of Labour in each province throughout Canada is responsible for enforcing the Occupational Health and Safety regulations (Dean et al., 2010). Quebec has the most protective and effective of these laws. In Quebec, the pregnant woman’s physician can at any time request l’Institut de Recherche Robert-Sauvé en Santé et en Sécurité du Travail (IRSST) take samples in any occupational environment where chemical exposure may occur (Ostiguy, 2012). These samples are then sent to a physician at the health department to determine if the exposure is safe or not safe for the pregnant woman. In Quebec pregnant women are considered “vulnerable workers” which can expedite this course of action (Ostiguy, 2012).

Discussion with authorities in British Columbia (WorkSafe BC) suggest that it would be very challenging to determine whether or not the laws are being upheld, as the ratio of occupational hygienists to industry is approximately 300 hygienists to 3,000,000 employers (Teo, 2012). Authorities in Ontario suggest similar challenges due to lack of funding for occupational hygienists (Labour, 2012). Although there are a number of potential sanctions put in place to deter employers from placing a pregnant worker in harms way either for herself or her unborn child, determining the extent to which these laws are upheld is extremely difficult (Teo, 2012).

The situation of an inadequate supply of occupational hygienists to assess workplace environments is untenable for accurate monitoring. The Quebec model where the pregnant woman’s contact with the physician generates a chain reaction for investigation of her workplace, leaves fewer woman unprotected. There is less chance in this model for a woman
to slip through the cracks of appropriate protection. The Quebec model combined with an updated published list of teratogenic chemicals, similar to the California model, is a direction that would best serve to protect pregnant women in potentially dangerous workplaces.

### 9.6 Summary

The study reported by Laslo-Baker et al. (2012) indicated that despite the fact that the pregnant mothers in their study experienced minimal symptoms of toxicity, detrimental effects were still evident in their offspring. In many provinces within Canada, the gap between what is written and the Occupational Health and Safety regulations with respect to protecting pregnant women and the extent to which these guidelines are upheld in industry are largely unknown.

Occupational Health and Safety laws are in place to protect pregnant workers against hazards but they do not delineate how employers must go about doing this. The laws are based on Occupational Health and Safety regulations but have been implemented differently based on the province in question. In Canada Quebec has the most comprehensive and effective legislation aimed at protecting the pregnant worker. Combining components from the legislation in Quebec with legislation from Proposition 65 in California may aid both employees and employers in implementing best practices to protect pregnant women. Currently, employers must decide for themselves how to best protect the pregnant worker while ensuring that they do not contradict the human rights laws. Giles (Insider, 2012) recommends that employers seek the advice of medical personnel or occupational hygienists to ensure that these provisions provide the appropriate level of protection.

Clinically, physicians and other health care professionals can use the information gained from epidemiological studies to inform women of childbearing age about the potential danger associated with exposure to organic solvents during pregnancy. Armed with such information, women will be more educated and may consider the effects not only of organic
solvent exposure, but exposure to other substances during pregnancy. Should prenatal exposure occur, the information from The Laslo-Baker et al. (2004) study, along with earlier research, may aid in the early detection of these young children so that intervention may assist them toward achieving their optimal level of functioning.
9.7 References


Insider (HRInsider.ca). (2012). *Protecting the pregnant worker: Drawing the line between safety and discrimination* (Article). [HRInsider.ca is available online as a paid membership service of Bongarde Media].


Appendices
Appendix A
MOTHERISK Intake Form

The Hospital for Sick Children  MOTHERISK Intake Form

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Work Phone</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Date of Birth</th>
<th>CVS</th>
<th>Yes</th>
<th>No</th>
<th>Amnio</th>
<th>Yes</th>
<th>No</th>
<th>Advised</th>
<th>Results</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Current MD Type</th>
<th>MD Phone</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CALLER</th>
<th>Contact Number</th>
<th>Identify</th>
</tr>
</thead>
</table>

**NOT PREGNANT:**
- General info: __________
- Planning: __________
- Retrospective: __________
- Breast-feeding: __________
- "LMP (d/m/y) __________ every __________ days"

**PREGNANCY**
- Currently: weight: __________ kg, lb, gestation: __________ wk, mos
- EDC (d/m/y) __________ by date(s) __________ by ultrasound __________
- GA: P, SA, TA, ectopic __________ mo, __________ gestation

<table>
<thead>
<tr>
<th>Defects in previous pregnancies</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most recent ultrasound in current pregnancy:</td>
<td>not yet</td>
<td>yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>weeks</th>
<th>reason</th>
<th>results</th>
</tr>
</thead>
</table>

**DRUGS**
- Infections & Chemicals - reverse

<table>
<thead>
<tr>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td>__________</td>
<td>__________</td>
</tr>
</tbody>
</table>

**EXPOSURE**
- baseline risk explained: yes | no | Risk no >1-3% | yes |
- Clinic date/time: __________
- Bring translator: __________
- Language spoken: __________
- DISCUSSED: folate __________ amount advised: __________
- ultrasound __________ MSDS requested: __________
- Referred to: NVP line | FAS line | HIV line |
- Referred back to MD for suggestions of medications: __________

**ADVICE**

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### Infectious Diseases

- Chlamydia
- Genital herpes
- EHV
- CMV
- Mycoplasma
- Group B strep
- HIV
- Hepatitis B
- Hepatitis C
- Shingles
- Syphilis
- Toxoplasmosis
- Pneumococcus
- Other:

Exposed only ☐  Infected ☐

Date of diagnosis: ❌

Disease clinically diagnosed (patient): ☐ yes ☐ no

Patient had disease in past: ☐ yes ☐ no ☐ unsure

### Symptoms (Patient)

Date of contact with infected person:

Date of lesions on infected person:

### Type of Contact

- Blood ☐
- Oral ☐
- Household ☐
- Lesions ☐
- Mucosal ☐
- Daycare ☐
- Sexual ☐
- Fecal ☐
- Hospital ☐
- Other:

### Breast-feeding Information

<table>
<thead>
<tr>
<th>Date of Birth</th>
<th>Number of Times Breastfed in 24 hr Period</th>
<th>BF Chapter</th>
<th>Hole</th>
<th>Briggs</th>
<th>Safe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age at Birth (wks)</td>
<td>Formula? Yes No</td>
<td>Soy? Yes No</td>
<td>Age Started</td>
<td>Age Started</td>
<td># Times/Day</td>
</tr>
<tr>
<td>Birth Weight (lbs oz)</td>
<td>#</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Reference Advice/Additional Information:

- [Irrelevant text]
Appendix B
Standardized Text: Initial Phone Contact, Exposed Mothers

**Standardized Phone Text**

- Dionne Laslo and myself, Dafna Knittel work with the Motherisk team at the Hospital for Sick Children.
- As you may remember, you were (seen/counseled) by the Motherisk program at HSC (remind them the last date of contact) about working with chemicals during pregnancy **PAUSE** (may need to remind about prior contact)
- We would like to invite you and your child to participate in a new study here at the hospital.
- We want to study how exposure in the work place to chemicals, specifically, organic solvents during pregnancy affects children’s development.
- No need to be alarmed, but we feel this is an important area that has not been well studied in the past
- We will be looking at physical development as well as language, intellectual, and social-emotional functioning.
- If you agree to participate, we will ask you to come to the Hospital for Sick Children where you and your child will work with our research team. Your child will be given a brief exam by a physician and then he/she will meet with our main investigator, Ms. Dionne Laslo/psychometrist, who will work with him/her on a number of brief tasks involving attention, learning, language, social-emotional adaptation, and general intelligence.
- No invasive procedures (i.e. no blood work) involved in this study.
- Ms. Laslo or the psychometrist will also work with you on tasks involving general intelligence and you will be asked to complete several questionnaires.
- Duration - approximately 1.5 to 2 hours for your child and approximately 30 minutes for yourself.
• Your participation would be very important to us and may help other families or even your family in the future.
• Pay for any transportation costs
• Would you be interested in participating?

If family is interested:
• I will mail a consent form to you to review, you do not need to send this back, and I will phone you in approximately one or two weeks to answer any further questions that you may have (the consent form will be explained to the mother again when she attends the scheduled session at HSC at which time the mother will be asked to sign the consent form prior to the family’s involvement in the study).
• We prefer to book during weekdays, but will conduct the assessment in the evening or on the weekend

Only if needed, explanations:

As you may know, organic solvents are chemicals that are widely used in various industries including the manufacturing and use of certain paints, plastic adhesives, dry-cleaning, and microbiological laboratories. We are attempting to see if children whose mothers were exposed to organic solvents during pregnancy perform differently than children whose mothers were not exposed to organic solvents during pregnancy. We will be looking at language, intellectual, and social-emotional functioning. There have been several studies that have suggested a link between exposure to organic solvents during pregnancy and physical problems in the newborn infant, however, there is a lack of research on how exposure to organic solvents affect later child development. We will look at both physical development (for example, growth compared to other children) as well as areas including language, intellectual, and social-emotional functioning.

We will be comparing a group of children who were exposed to organic solvents during pregnancy with a group of children who were not exposed to organic solvents during pregnancy.
Appendix C
Motherisk Follow-Up Form

Initial data on phone:
Mother’s FIRST NAME: ___________________ LAST NAME ___________________
Mother’s date of birth: _________________________________________________________
CHILD’S NAME ____________________________________________________________
Child’s date of birth: _________________________________________________________
Child’s gender: Girl / Boy
Telephone (H): ___________________ (W) _______________________
RACE: White African American Indo-Asian Hispanic Oriental Asian

<table>
<thead>
<tr>
<th>Social Drugs/Others</th>
<th>Dose</th>
<th>Frequency</th>
<th>Started</th>
<th>Stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol/wine</td>
<td>______ ounce [ ]</td>
<td>per day [ ] week [ ]</td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>__________ glass [ ]</td>
<td>per day [ ] week [ ]</td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>__________ bottle [ ]</td>
<td>per day [ ] week [ ]</td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td>______ cigarettes</td>
<td>per day [ ] week [ ]</td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heat Exposure:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Tub</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electric Blanket</td>
<td></td>
<td>per day [ ] week [ ]</td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td>per day [ ] week [ ]</td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td>per day [ ] week [ ]</td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
<tr>
<td>Yes [ ] no[ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

163
Occupation during pregnancy _________________________________________
Commenced Work: _________________ Stopped Working: _________________
Reason for stopping: _________________________________________________
Exposures:
Chemical ( ) no ( ) yes
Computer ( ) no ( ) yes
Noise / vibration ( ) no ( ) yes
SES – Family income: 1=10,000 – 30,000 2=31,000 – 50,000 3=50,000 +
Appendix D
Motherisk Pregnancy Follow Up Form

Pregnancy Follow Up
MOTHERISK PROGRAM

ID NUMBER:
Date of Interview:
Interviewer:

A. GENERAL
Mother’s FIRST NAME ______________ Street Address ______________
Mother’s LAST NAME ______________ City/Province ______________
Telephone (H) ____________ (W) ______ Postal Code ______________

B. PREGNANCY OUTCOME

How did your pregnancy end? p Live birth p Miscarriage (<20 wks) p Fetal Death (≥20wks) p Elective abortion

If miscarriage, fetal death or elective abortion: If live birth: p
boy p girl

At how many weeks? ____________ Child’s FIRST NAME ____________
Were defects detected? refer Yes No p Child’s LAST NAME ____________
If Yes, describe__________________________ Child’s DATE OF BIRTH__________
______________________________________ Child’s doctor ______________
______________________________________ Street address ______________

How? By p ultrasound p amniocentesis

done at ________ weeks telephone __________________

C. DISEASES COMPLICATING PREGNANCY

Details: diagnosis onset

medication/doses hospitalization?
Amniotic fluid alterations No Yes ________________________________
Cancer NoYes ________________________________
Cardiovascular NoYes ________________________________
Central nervous system No Yes ________________________________
Dermatology NoYes ________________________________
### Ears, eyes, nose, throat
- No
- Yes

### Endocrine
- No
- Yes

### Gastrointestinal
- No
- Yes

### Genito-urinary
- No
- Yes

### Hematology
- No
- Yes

### Infectious Disease
- No
- Yes

### IUGR/growth problems
- No
- Yes

### Musculo-skeletal
- No
- Yes

### Psychiatric
- No
- Yes

### Respiratory
- No
- Yes

### OTHER

---

**TELEPHONE LOG**

<table>
<thead>
<tr>
<th>DATE/TIME</th>
<th>NUMBER DIALED</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**D. EXPOSURES DURING PREGNANCY**

- Did you use any herbal preparations?
- Did you use any vitamins (prenatal or other supplements)?
- Did you use anything for allergies, anxiety, colds, constipation, depression, diarrhea, headache, heartburn, pain, weight loss?

---

**Over-the-Counter/Prescription medications and Radiation**

<table>
<thead>
<tr>
<th>Drug Name or Radiation Type</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Dose (mg,g,mL)</th>
<th>Frequency (od,qhs,bid,tid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>ongoing</td>
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<td></td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Indication for Medication</th>
<th>Prescribing Physician</th>
<th>Details about medical condition</th>
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</thead>
<tbody>
<tr>
<td>Social Drugs/Others</td>
<td>Dose</td>
<td>Frequency</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Ethanol wine [ ] p no</td>
<td>_____ ounce [ ]</td>
<td>per day [ ] week [ ]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weekend [ ] month [ ]</td>
</tr>
<tr>
<td></td>
<td>liquor [ ] p no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>_____ glass [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>beer [ ] p no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>_____ bottle [ ]</td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td>p no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>_____ cigarettes</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>p no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>_____ per day [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>week [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>weekend [ ] week [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>month [ ]</td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>p no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>_____ per day [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>week [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>weekend [ ] week [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>month [ ]</td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td>p no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>_____ per day [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>week [ ]</td>
<td></td>
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<tr>
<td></td>
<td>weekend [ ] week [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>month [ ]</td>
<td></td>
</tr>
<tr>
<td>Heatjaccuzzi [ ] p no</td>
<td>_____ per day [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>week [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
<tr>
<td>electric blanket [ ] p no</td>
<td>_____ per day [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>week [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>p no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>_____ per day [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>week [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>p no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>_____ per day [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>week [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>weekend [ ] month [ ]</td>
<td></td>
</tr>
</tbody>
</table>

Occupation during pregnancy (what does she do?) ________________________________

Started ______________________  Stopped ______________________

Reason for Stopping

EXPOSURES?

chemical no yes: ________________________________

computer no yes: ________________________________

radiation no yes: ________________________________

noise/vibration no yes: ________________________________

E. TESTS DURING PREGNANCY

1. Triple screening no yes: at _____ weeks Reason _______

2. Amniocentesis no yes: at _____ weeks Reason _______
3. Glucose Tolerance Test  no  yes:  at _____ weeks Reason ________

4. Ultrasound  no  yes:  at _____ weeks Reason ________
   at _____ weeks Reason ________
   at _____ weeks Reason ________

5. Chorionic villus sampling  no  yes:  at _____ weeks Reason ________

6. Other _____________________  no yes:  _____________________
   at _____ weeks Reason _____________________

RESULTS: # ____:  _______________________________________________________
# ____:  _______________________________________________________
# ____:  _______________________________________________________
# ____:  _______________________________________________________
# ____:  _______________________________________________________

F. DELIVERY INFORMATION

Maternal
Weight pre-pregnancy ______ lb ______ kg
   gain ________ lb __________ kg
Total length of labour ________ hours
PROM? p no  p yes: ______ hours
   before onset of labour
   (Premature Rupture of Membranes)

Method  p vaginal, vertex  p C/S emergency
   p vaginal, breech  p C/S repeat  p C/S
scheduled
Assistance:  p vacuum
   reason: ______________________
   p forceps

Hemorrhage? no  yes
Transfusion? no  yes
Pain relief? Anaesthetics no  yes
   epidural  no
   yes
   analgesic  no
   yes
   specify:

Neonatal
Hospital/City __________________________

Gestational age at birth ________ weeks
   ________ days
Birth weight ________lb ________ oz (__________ grams)

1 oz=28.4 g

Head Circumference ________ cm
Apgar scores 1 minute ______ 5 minute ______

   __________ Appearance
   __________ Pulse
   __________ Grimace
   __________ Muscle activity
   __________ Respiration

Fetal Monitoring  no  yes
   external [ ] internal [ ]
   explain

Fetal distress  no  yes
   explain

Meconium  no  yes
You originally called the Motherisk Program to find out whether your exposure increased your baby’s risk for being born with a major birth defect. At that time, we explained to you that every pregnancy has a 1-3% baseline risk for malformations.

For our own documentation, which will help other women exposed to the same drug that you were exposed to, would you share with us whether your child was born with any birth defects?

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G. NEONATAL HEALTH

Health in hospital intensive care? no yes Home at: _________ days

Breast feeding no yes stopped ______ months

Medication during lactation? no yes (specify details in section D)

Name: ____________________________________________________________

Infant side effects? no yes:_________________________________________

Formula feeding no yes started _____ months stopped _____ months

Solids not yet yes started ______ months type: _________________________

Problems with feeding? no yes explain: ________________________________

Details: diagnosis onset medication dose hospitalization?

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<td>Yes</td>
<td>__________________</td>
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<td>Dermatology</td>
<td>No</td>
<td>Yes</td>
<td>__________________</td>
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<tr>
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<td>Yes</td>
<td>__________________</td>
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<td>Yes</td>
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<td>__________________</td>
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<tr>
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<td>Yes</td>
<td>__________________</td>
</tr>
<tr>
<td>Respiratory</td>
<td>No</td>
<td>Yes</td>
<td>__________________</td>
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</table>
OTHER

H. MILESTONES

At what age did the infant first: Normal range
Smile (recognition) ___________ [2 months] Infant’s age at follow-up ___________ months
Lift head on own ___________ [3 months] Infant’s weight
Sit unaided _______________ [6-8 months] as of: follow up last MD visit
Crawl _______________ [8-10 months] Infant’s height/length ______ cm ( _____ inches)
Stand on own _______________ [8-10 months] as of: follow up last MD visit
Speak first word _______________ [8-12 months]
Walk unaided _______________ [12-15 months] Last MD visit: ____________________________ (date or baby’s age)

I. CONSENT

We would like to send a letter to your child’s doctor to confirm medical details of this follow-up. May we have your verbal permission to send this?

OBTAINED CONSENT? No Yes

Date letter sent: ____________________________ Date letter received: ____________________________
Appendix E
Consent Form

Child Neurodevelopment Following in utero Exposure to Organic Solvents

Investigators:
Primary Investigator: Dionne Laslo, Ph.D. Candidate
Institute of Medical Science/University of Toronto
Hospital for Sick Children
(416) 813-7284, ext. 6

Study Coordinator: Dafna Knittel - Keren
Hospital for Sick Children
(416) 813-7284, ext. 7

Primary Supervisors:
Dr. Gideon Koren
Hospital for Sick Children
(416) 813-5778

Dr. Maru Barrera
Hospital for Sick Children
(416) 813-6819

Purpose of the Research:
Organic solvents are chemicals that are widely used in various industries including the manufacturing and use of certain paints, plastic adhesives, dry-cleaning, and microbiological laboratories. The goal of this study is to see if there are any long-term risks associated with occupational exposure to organic solvents. We are attempting to see if children whose mothers were exposed to organic solvents during pregnancy have any problems in language, intellectual, or social-emotional functioning. There have been several studies that have suggested a link between exposure to organic solvents during pregnancy and physical problems in the newborn infant, however, there is a lack of research on how exposure to organic solvents affect later child development.

Description of the Research:
Your child will be asked to work with Ms. Laslo on several tasks that will be used to assess attention, learning, hearing, language, social-emotional adaptation, and general intellectual functioning. The testing will take approximately 2.5 - 3 hours depending on the pace of your child. No invasive procedures, such as blood work will be involved in this study. In addition, you (the parent) will be asked to complete several questionnaires about your child’s developmental history, academic, behavioral, and social-emotional functioning. Ms. Laslo will also conduct a brief assessment of your level of intellectual functioning, which will take approximately 30 minutes. We ask this of each mother in order to estimate their child’s expected level of development and because parental intellectual functioning is a useful predictor of a child’s expected development. The results from this brief assessment will be confidential, will only be used for research purposes and will not be included in your child’s report. During the assessment you are encouraged to ask Ms. - any questions about the study, the tasks involved, or the questionnaires at any time.

Potential Harms and Benefits:
There are no known risks associated with participating in this study, in fact, your child might find some of the tasks interesting. After you and your child have completed your participation in the study, a letter will be sent to you describing the results, which you might find interesting and useful. If a problem is identified during testing (that was not previously identified), we will discuss these findings with you and provide you with recommendations and/or referrals (if needed). As there is little information known about the effects of organic solvent exposure during pregnancy, your participation in this study will further our understanding and help to benefit others in the future.

Confidentiality:
The information provided by you and your child will be kept in strict confidentiality and will be pooled with information from other study participants. All information from testing will be recoded so that the results and names cannot be matched. We will use the results only for research purposes. Upon completion of the study, we will provide you with a report that outlines the findings for you. We will not release any information without your consent. With your permission, we will pass on raw scores only to persons involved in the care of your child. We recommend that a registered psychologist or physician interpret the results.

Participation:
Participation in research is voluntary. If you choose to participate in this study it is important that you explain the goal of the research and the tasks involved to your child. Furthermore, if you decide to participate it is also important that both you and your child agree to be involved in the study. If you choose not to participate, you and your family will continue to have access to the support, facilities and treatment through the Hospital for Sick Children.

Consent:
I acknowledge that the research procedures described above have been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at The Hospital for Sick Children for my child and for other members of my family. As well, the potential harms and discomforts have been explained to me and I also understand the benefits (if any) of participating in the research study. I know that I may ask now, or in the future, any questions I have about the study or the research procedures. I have been assured that records relating to my child and my child’s care will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission unless required by law.

I hereby consent for my child: ____________________ to participate.

Name of Parent (Please print clearly)

__________________________________________

Signature of Parent

Name of person who obtained consent

__________________________________________

Signature

__________________________________________

Date

The person who may be contacted regarding this Study: Dionne Laslo, Ph.D. Candidate
Department of Clinical Pharmacology & Toxicology
Hospital for Sick Children
(416) 813-7284. ext. 6
Appendix F
Exposure Details Form

Please complete this form with the details of your exposure to organic solvents during your pregnancy. This information is very important, please try to complete this form as thoroughly as possible. If you have difficulty confirming the chemical(s), please provide the commercial name or any identifying information about the source of the chemical (for example, manufacturers name). Please contact our office at (416) 813-7284, ext. 8 if you require any help with this form. This form should be completed and mailed (self addressed stamped envelope is included) or faxed to our office, ATTENTION Dafna Knittel-Keren at (416) 813-7562.

Name: ________________________________
(Please print clearly)

Date: __________________________________________
_________________________________________

Chemical Exposures

Chemical(s): __________________________________________
________________________________________

Occupation: __________________________________________

EXPOSURE

Type: direct secondary

Where: factory office home school other _____________________________

Route: skin oral inhalation other _____________________________

Duration: minutes hours days other _____________________________
How many days per week____________________________

Length of exposure during pregnancy (days per week/months)_________________

Which weeks were you exposed over duration of pregnancy (i.e., weeks 2-25)______

_______________________________________________________________

Barrier: gloves mask respirator fumehood
other______________________________

Side effects: nausea vomiting diarrhea rash headache tremors blurred vision
other______________________________
Appendix G
Child Neurodevelopment Following
In Utero Exposure to Organic Solvents: Follow-Up Letter

Dear Ms.….,

Thank you for your interest and participation in the study titled Child Neurodevelopment Following in utero Exposure to Organic Solvents with the Motherisk Follow-Up Program at the Hospital for Sick Children. By participating you have helped broaden our knowledge base about the effects of exposure to organic solvents during pregnancy. Moreover, we are now able to provide important information regarding potential risks associated with exposure to organic solvents during pregnancy to other pregnant women, health care providers and governing agencies.

We have included a copy of the results from the study, which we hope you will find interesting. Please do not hesitate to call the Motherisk Program at 416 - 813-8379 if you have any questions.
Thank you again,

__________________
Dionne Laslo-Baker  Dafna Knittel-Keren
Ph.D. Candidate  Study Coordinator
Appendix H

Physician Completed Exposure Details Form: Confirmation of Exposure Data

Name: ____________________________________________________________
(Please print clearly)

Date: ____________________________________________________________

Chemical Exposures

Chemical(s): _____________________________________________________

_______________________________________________________________

Occupation: ______________________________________________________

EXPOSURE

Type: direct secondary

Where: factory office home school

other ___________________________________________________________

Route: skin oral inhalation

other ___________________________________________________________

Duration: minutes hours days

other ___________________________________________________________

How many days per week_________________________________________

Length of exposure during pregnancy (days per week/months)__________

Which weeks were you exposed over duration of pregnancy (i.e., weeks 2-25)____

_______________________________________________________________

Barrier: gloves mask respirator fumehood
Side effects: nausea vomiting diarrhea rash headache tremors blurred vision
other__________

NEUROBEHAVIORAL STUDY (MEDICAL EXAMINATION)
Child Neurodevelopment Following in utero Exposure to Organic Solvents

ID: ______________________________________ DATE: __________________________

First name__________________ Middle initial ______ Last Name_______________

Date of Birth Day_____Month_____Year______ Age________ Sex____

History of Present Illness:

Past Child History:

Birth History:

One Minute ______ Five Minute ______ Birth Weight ______

Post Natal Complications:

Family History:
**Genetic History:**

**Social History:**

**Allergies:**

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Babinski Response

Sensory Systems

Cerebellar System
Appendix I
Distribution of Test Scores for Cognitive and Language Variables That Were Significantly Different Between the Exposed and Non-Exposed Child Groups

Figure I-1. Distribution of scores on the WISC-III Verbal IQ score.
Figure I-2. Histogram of scores on the WISC-III Digit Span sub-test scaled score.
Figure I-3. Distribution of scores on the WISC-III Digit Span.
Figure I-4. Histogram of scores on the WISC-III Digit Span sub-test scaled score.
Figure I-5. Distribution of scores on the CELF-R Recalling Sentences percentile.
Figure I-6. Histogram of scores on the CELF-R Recalling Sentences percentile.
Figure I-7. Distribution of scores on the CELF-3 Expressive Language percentile.
Figure I-8. Histogram of scores on the CELF-3 Expressive Language percentile.
Figure I-9. Distribution of scores on the WPPSI-R Verbal IQ score.
Figure I-10. Histogram of scores on the WPPSI-R Verbal IQ score.
Figure I-11. Distribution of scores on the WPPSI-R Information sub-test scaled score.
Figure I-12. Histogram of scores on the WPPSI-R Information sub-test scaled score.
Figure I-13. Distribution of scores on the WPPSI-R Vocabulary sub-test scaled score.
Figure I-14. Histogram of scores on the WPPSI-R Vocabulary sub-test scaled score.
Figure I-15. Distribution of scores on the WPPSI-R Sentences sub-test raw score.
Figure I-16. Histogram of scores on the WPPSI-R Sentences sub-test raw score.
Figure I-17. Distribution of scores on the PLS-3 Auditory Comprehension scaled score.
Figure I-18. Histogram of scores on the PLS-3 Auditory Comprehension scaled score.
Figure I-19. Distribution of scores on the PLS-3 Auditory Comprehension Age Equivalent.
Figure I-20. Histogram of scores on the PLS-3 Auditory Comprehension Age Equivalent.
Appendix J

Distribution of Test Scores for Behavioral Functioning, Temperament, and Motor Skills That Were Significantly Different Between the Exposed and Non-Exposed Child Groups

Figure J-1. Distribution of scores on the Conners Parent Rating Scale DSM IV Criteria for symptoms of ADHD.
Figure J-2. Histogram of scores on the Conners Parent Rating Scale DSM IV Criteria for symptoms of ADHD.
Figure J-3. Distribution of scores on the Grooved Pegboard non-dominant hand.
Figure J-4. Histogram of scores on the Grooved Pegboard non-dominant hand.