Phthalate Exposure in a Canadian Birth Cohort at Three Months of Age: Exposure Sources and the Influence of Socioeconomic Status

by

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B.A. (Health Sciences), Simon Fraser University, 2010

Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of
Master of Science

in the
Faculty of Health Sciences

SIMON FRASER UNIVERSITY

Spring 2012

Approval

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Abstract

Exposure to ubiquitous plasticizers known as phthalates may contribute to the development of an inflammatory response and be a factor in the development of allergic disease through direct or adjuvant mechanisms. Some of the important exposure pathways of phthalates include ingestion, injection, inhalation, and dermal absorption.

The Canadian Healthy Infant Longitudinal Development (CHILD) Study is a multicentre, multidisciplinary, longitudinal, population-based birth cohort study of 5,000 children enrolled “pre-birth” and followed for five years. The purpose of this birth cohort is to identify and quantify determinants of asthma and allergy in early childhood.

We examined associations between phthalate exposures in the indoor environment, including indoor furnishings, occupation, household care products and personal care products with seven phthalate metabolites (monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), monoethyl phthalate (MEP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) and monoethyl phthalate (MMP)) in urine from 578 CHILD subjects at three months of age. Additionally, we looked at their relationships with socio-economic status.

We found higher levels of urinary phthalate metabolites associated with use of household product, such as bathroom tile cleaner; air fresheners, usage of plastic and personal baby care products such as baby wipes. Associations between household income and the levels of urinary phthalate metabolites concentrations were also found.

Keywords: phthalate; questionnaire; urine; product; plastic; income; regression, censored

Dedication

This thesis is dedicated to my parents, who taught me that even the largest task can be accomplished if it is done one step at a time.

Acknowledgements

I would like to express my sincere gratitude to my mentor Dr. Tim Takaro for the continuous support of my MSc study and research, for his patience, motivation, enthusiasm, and immense knowledge. I could not have imagined having a better mentor for my MSc study.

This thesis would not have been possible without the guidance and support from Dr. Leilei Zeng and Dr. Ryan Allen.

I would like to thank AllerGen NCE Inc. for funding, and the Canadian Health Infant Longitudinal Development (CHILD) Study, Environment Canada and Health Canada for advisory and data support.

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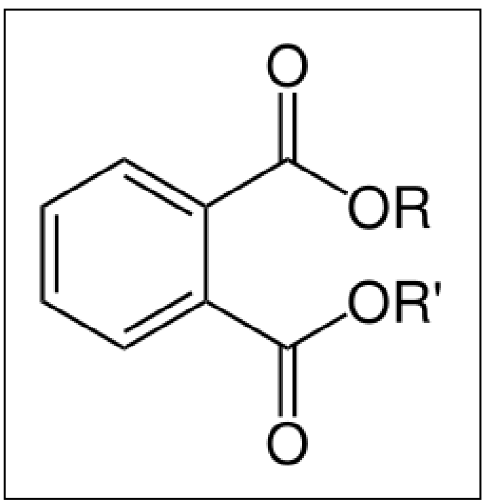
1. Introduction

1.1 Background

Phthalates, a family of semi-volatile synthetic chemical compounds that share a similar chemical structure (Figure 1.1); have been widely used as plasticizers for the past 75 years. (Kamrin, 2009) The variations in the two carbon arms lead to variations in their physical and chemical properties. Phthalates with high molecular weight contain longer carbon chains, and have been used in building and furnishing materials, food packaging, and plastic tubing (CHRP, 2008). Phthalates with lower molecular weight contain shorter carbon chains and have been used as a scent stabilizer in a variety of personal care and cosmetic products (CHRP, 2008). Since phthalates do not chemically bond to plastics, they can leach into the environment.

Figure 1.1 Chemical structure of phthalates



The general population is regularly exposed to phthalates (CDC, 2011). Phthalates have relatively short biologic half-life, ranging from 3 to 12 hours (Hoppin, 2004). However, their ubiquity in the environment and great number of people being exposed provides reason to believe there could be a substantial impact on human health from phthalates exposure. Phthalates have being found in dust and air samples not only in commercial indoor environments, but also in residential indoor environments. Other studies have also shown that there are phthalates in consumer milk, food and water (Zhu et al., 2006; Cirillo et al., 2011; Rudel et al., 2011; Montuori et al., 2008).

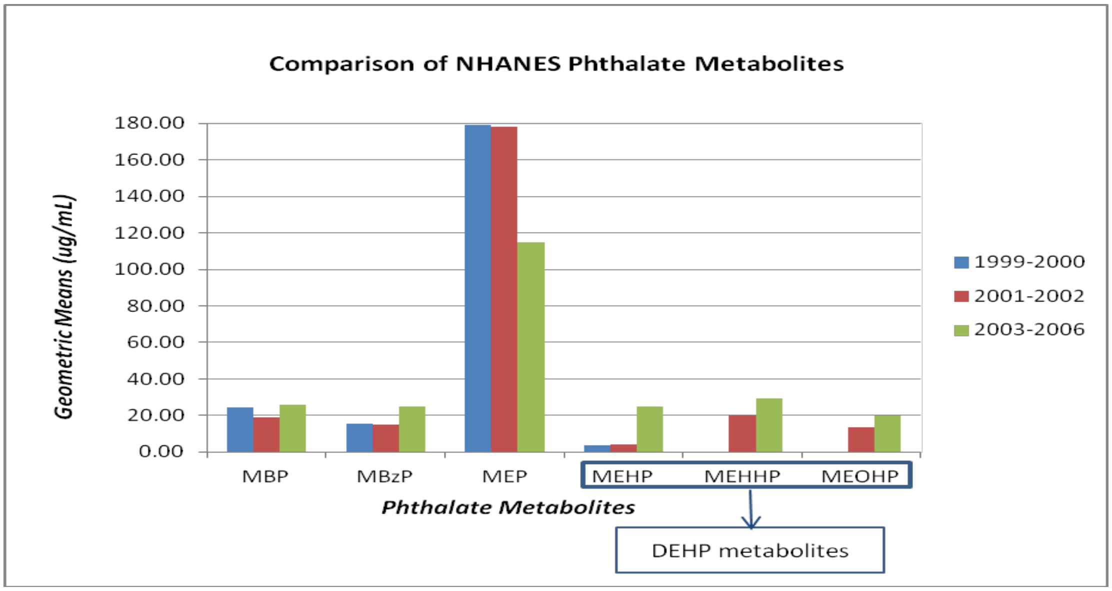
Many epidemiological studies have estimated personal exposure by measuring phthalates and their metabolites in breast milk, urine, umbilical cord blood, and semen (Swan et al., 2005; Hoppin et al., 2004). Table 1 lists chemical names, abbreviations, molecular weight and chemical abstract registry (CAS) for specific phthalates that were the focus of this research.

Table 1.1 Phthalates and their metabolites

Parent Compound	*Metabolite*	*Molecular weight*	*CAS*
Dimethyl Phthalate (DMP)	Mono-methyl phthalate (MMP)	194.18	131113
Butylbenzyl Phthalate (BBzP)	Monobenzyl Phthalate (MBzP)	312.39	85687
Dibutyl Phthalate (DBP)	Mono-n-butyl Phthalate (MBP)	278.34	84742
Diethyl Phthalate (DEP)	Monoethyl Phthalate (MEP)	222.24	84662
Di-2-ethylhexyl Phthalate (DEHP)	Mono-2-ethylhexyl Phthalate (MEHP)	390.57	117817
	Mono-2-ethyl-5-hyroxyhexyl Phthalate (MEHHP)		
	Mono-2-ethyl-5-oxohexyl Phthalate (MEOHP)		

Several researchers have utilized the U.S. National Health and Nutrition Examination Survey (NHANES), the largest national database measuring health and nutrition of the U.S. population, to examine human exposure to phthalates. Since 1970, five phases of the NHANES have been completed; phthalates have been a part of the survey in the majority of the phases: 1999-2002, 2001-2002, 2003-2004, and 2005-2006. As shown in Figure 2, MEP, MBP, MBzP, and MEHP were found in more than 75% of the NHANES 1999-2000 samples, which suggested widespread exposure in the U.S. population. (Silva et al., 2004)

Figure 1.2 Comparison of NHANES Phthalate metabolites*



* This table was produced prior to the CDC phthalate concentration adjustment

1.2 Exposure: Levels, Sources and Routes

Humans can be exposed to phthalates through many different routes such as ingestion, injection through medical supplies, absorption through skin, and inhalation of gas and airborne fine particles that have been contaminated with phthalates.

1.2.1 Ingestion – Dust

The ‘incidental consumption’ from ingestion of household dust is a likely pathway for toddlers (Wu et al., 2007; Jones-Otazo et al., 2005).

The ingestion of household dust for children has been shown to be more than double the amount for adults (EPA, 2007). Many researchers have hypothesized that the reason for this relationship was due to the proximity to the floor, and also their frequent hands-to-mouth behaviour of young children. Guo et al. (2011) compared the daily intakes level of several phthalate esters from indoor dust between cities in China and cities in the United States and found that toddlers consistently had the highest intake levels for all examined phthalate esters (DEP, DBP, BzBP, and DEHP) across all age groups (infants, toddlers, children, teenagers, and adults).

1.2.2 Ingestion – Food packaging

Several studies have shown the potential contamination from food packaging to our food supplies (Cirillo et al., 2011; Rudel et al., 2011).Cirillo et al. (2011) studied packed school meals in Italy, both before processing and after packaging food samples were collected. Cirillo et al. (2011) reported that 92% of the samples had detectable DEHP (before packaging median concentration ranged from 111.4-154.8 ng/g ww, after packaging median ranged from 127.0 – 253.3 ng/g ww) and 76% with detectable DBP (before packaging median concentration ranged from 32.5 – 59.5 ng/g ww, after packaging median ranged from 44.1 – 80.5 ng/g ww).

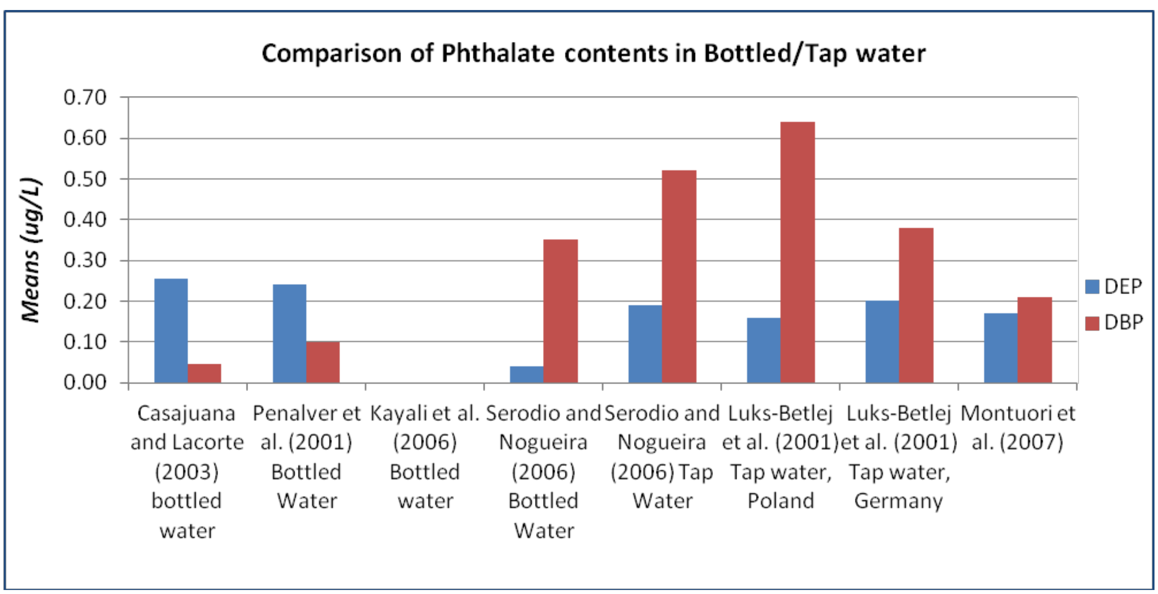
Rudel et al. (2011) conducted a food intervention study in California to evaluate the contribution of food packaging to phthalate exposure. Rudel et al (2011) recruited 10 adults (median age = 40.5 years) and 10 children (median age = 7 years). Subjects started with their normal diet followed by three days of a “fresh food only” intervention diet, and finally, returned back to their normal diet. Two urine samples were collected for each phase of the intervention study for each subject. During the fresh food interventions, the geometric mean concentrations for DEHP metabolites were reduced by 53-60%, which suggested that food packages are an important source for DEHP.

Similar results were found in the purchased pre-packed lunch boxes from 10 stores in Osaka, Japan. After Tsumura et al. (2001) analyzed all purchased samples, BBP (0.1 – 41.3 ng/g) and DEHP (12 – 304 ng/g) were found in all lunch box samples. Tsumura et al. (2001) indicated the main source of high DEHP concentration were disposable PVC gloves, which were used in the preparation of lunch boxes. Sterilizing alcohol sprays were found to increase the migration of DEHP to rice (0.05 – 2.03 mg/kg), croquettes (0.33 – 2.45 mg/kg) and radishes (11.1 – 18.4 mg/kg).

DBP, BBP, and DEHP were also found in butter and margarine samples that were collected in Canada (Page & Lacroix, 1992). These phthalates were transferred from the packaging wrap paper, since they were added into the aluminum foil paper during the laminating process (Page & Lacroix, 1992). Another interesting finding was that the DEHP background level which was examined prior to the packaging process was much higher in butter samples, than in margarine, this indicated the existence of contamination through the production process (Page & Lacroix, 1992). There hasn't been any recent data regarding this contamination through butter and margarine packaging. However, Freire et al. (2006) tested food products that were packed in PVC, which were collected from Brazilian retail markets and DEHP were found in approximately 50% them.

Since early 80s, the bottled water industry has grown significantly (Griffin, 2009). Several studies have tested bottled water and tap water; DEP and DBP were found in all samples from different studies (Figure 3). These bottles were made of Polyethylene terephthalate (PET). Phthalate concentrations for PET water bottles were 20 times higher than the glass bottled samples, longer storage time is associated with higher phthalate concentrations in water samples (Montuori et al., 2008). Montuori et al. (2008) indicated the correlation between the use of PET bottles and the concentration of phthalates in the water sample. DEP had the relative similar concentration range between tap water and bottled water; however, DBP had the highest concentration in tap water, which may due to contamination through water processing steps, such as PVC tubing etc. (Montuori et al., 2008)

Figure 1.3 Comparison of phthalate contents in Bottled or Tap water



1.2.3 Ingestion – Medication

Phthalates have also been added to the enteric coatings of oral medications to control the timing of the active ingredients being released (Hernándex-Díaz et al., 2009, Koch et al., 2005). Hernándex-Díaz et al. (2009) analyzed a subset of NHANES data, which contains medication usage and urinary phthalate metabolite information. Hernándex-Díaz et al. (2009) identified *a priori* four medications (Mesalamine, didanosine, omeprazole, and theophylline), that potentially contained phthalates as a part of the non-active ingredient. For these four medications, users' urinary phthalate metabolite concentrations were statistically higher than non-medication users' urinary phthalate metabolite concentrations. Mesalamine users' urinary MBP phthalate metabolite concentrations were 50 times greater than non-users (Hernándex-Díaz et al., 2009). In a controlled human DBP exposure study seven male and ten female volunteers with aged 9 – 59 years were recruited (Seckin et al., 2009). Each volunteer was given one herbal medication and one capsule containing 3600ug of DBP. Urine samples were collected for each volunteer: before medication ingestion, within 24 hours ingestion, and after 24 hours of ingestion. Seckin et al. (2009) analyzed the within 24 hours ingestion urine sample, and converted MBP concentration to its parent compound DBP, and approximately 78% of the DBP (2248ug) were found in the within 24 hours ingestion urine samples. This level is much higher than the tolerable daily intake level of 10 ug/kg b. w. the level that adverse effects of MBP were observed in rats (Seckin et al., 2009).

1.2.4 Dermal – Personal care products

Based on the U.S. Food and Drug Administration (US FDA) regulations on cosmetics, manufacturers are not required to label all chemical ingredients – due to trade secrets – and they may use any raw material as an ingredient (FDA, 2005). These ingredients are not subject to FDA pre-market approval, and the final product can be marketed without FDA approval. (FDA, 2005) There is also no existent cosmetic safety committee, and FDA (2005) has no authority to force recall cosmetics. Due to the U.S. Food, Drug, and Cosmetic Act 1938, this multi-billion dollar cosmetics / personal care product industry has been allowed to self-regulate through an industry funded, and self-police cosmetics ingredient review panel. According to Environmental Working Group

(EWG), more than 80% of the ingredients are not assessed for safety. EWG tested 72 cosmetics / personal care products, almost 80% of tested products contain phthalates and none of them were listed as ingredients (EWG, n.d.). Phthalates have been used in personal care products as scent stabilizers, and masked under the “parfum” or “fragrance”. They can also be found in children’s care products, such as shampoo, bubble bath, lotion, among others (Sathyanarayana et al., 2008).

Several epidemiological research studies have shown correlations between personal care product usage and urinary metabolite concentrations. Duty et al. (2005) studied 406 men age between 20 to 54 years old from an ongoing semen quality study. Urine samples were collected on the same day that questionnaires were administered. Results from their multiple regression shows the urinary MEP phthalate metabolite concentrations were 2.57 times greater ($P<0.0001$) among men who used cologne than non-users, whereas approximately 1.70 times higher ($P=0.02$) among men who used after-shave than those who did not use. A similar study has also been completed with a female cohort. Just et al. (2010) recruited 186 inner-city, third-trimester, minority, New York City women. Just et al. (2010) found women who reported perfume use had 2.3 times greater ($P<0.001$) urinary MEP phthalate metabolite concentration, which is comparable with Duty et al. (2005) results with a male cohort.

1.2.5 Occupation

Another concern of phthalate exposure is through occupational exposure, especially among manicurists, who are more likely to be exposed to DBP through both inhalation and dermal contact due to work practices and their exposure to nail products (DBP have been added to nail products for durability and chip prevention) (Houlihan & Wiles, 2000). Kwapniewski et al. (2008) explored 40 manicurists’ exposure to DBP in and around Boston. Pre- and post-shift urine samples were collected from each subject on a single working day. There was a statistically significant cross shift increase in specific gravity adjusted MBP concentrations by 17.4 ng/ml ($p=0.05$). Interestingly, glove use had a protective effect on exposure to MBP ($p=0.04$).

1.2.6 Medical supplies

Because of its unique set of properties, phthalates have also been added to medical equipment to increase the flexibility of the equipment. Phthalates, however, are not chemically bound to polyvinyl chloride (PVC), and they can easily absorb into a different media such as blood products or even medication (Tickner et al., 2001). Studies have suggested the existence of hospital-based contaminations. DEHP was one of the phthalates that was a known additive in hospital PVC medical devices (Tickner et al., 2001). Vandentorren et al. (2011) collected urine samples in the delivery room from 250 French pregnant women. The levels of Di-(2-ethylhexyl)-phthalate metabolites were compared between subjects who were having natural delivery, or Caesarean/forceps delivery. Vandentorren et al. (2011) found Di-(2-ethylhexyl)-phthalate metabolites concentration for women who had caesarean sections or forceps-assisted deliveries were statistically higher than the subjects who had natural deliveries attributed to the usage of medical equipment.

Inoue et al. (2005) presented results from a Japanese study with 78 blood products that were collected from the Japanese Red Cross Society, the DEHP (1.8 – 83.2 ug/ml) and MEHP (0.1 – 9.7 ug/ml) phthalate concentration were positively correlated with the length of time a blood product was stored in a bag that contains PVC. These results indicated that humans can also be exposed to phthalates through blood transfusion. We should also pay more attention to Neonatal Intensive Care Unit (NICU) babies since they have higher daily contact with hospital equipment. Based on the medical product usage and DEHP concentration, Green et al. (2005) examined 54 neonates who were admitted to the hospital NICU, neonates were divided into DEHP-low, DEHP-medium, and DEHP-high exposure levels. Green et al. (2005) found positive correlation between MEHP metabolite concentration and the DEHP exposure levels, with concentration levels of 4 ng/ml, 28 ng/ml, and 86 ng/ml respectively. Similar results were found by Weuve et al. (2006) that both MEOHP and MEHHP metabolite concentration were 13 times higher in the high exposure group than in the lower intensiveness group ($p \leq 0.007$).

1.2.7 Inhalation

Phthalates have also been widely used indoors on surfaces, such as PVC flooring and furniture. Because they are non-binding, phthalates can easily leach into other environments, and can be found in dust samples (Bornehag et al., 2005; Kavlock et al., 2002). PVC flooring is popular due to design, protection and hygiene, low maintenance and durability (CPSI, n.d.). DEHP have been found in dust samples that were collected from different countries (Becker et al., 2004; and Fromme et al., 2004; Oie et al., 1997; Rudel et al., 2003) with median concentrations ranging from 340 ug/g to 858 ug/g. Bornehag et al. (2005) explored indoor phthalate levels in 390 homes in Sweden, and indicated a statistically significant positive correlation between the PVC flooring covered area and the indoor DEHP and BBzP phthalate level in dust samples. As well, the more rooms with PVC flooring or vinyl walls, the higher the indoor phthalate levels in the dust sample.

Other than being used in building supplies, phthalates can also be found in electronic devices and cable insulated coverings, as found by Rakkestad et al. (2007) who examined 14 different Norwegian indoor environments. They found a computer room in a university that had the highest levels of total phthalates in dust.

Phthalate concentrations in indoor air and dust have been used as an indicator for indoor phthalate levels. Researchers in Canada have found the differences between age of subjects and their DEHP indoor exposure levels. Chan & Meek (1994) observed a positive association between DEHP indoor concentration and ages that were younger than 11, and negative correlations when subjects were older than 11, this may be due to the differences in exposure routes, as well as proximity to floors and hand-to-mouth behavior in young babies. An additional explanation for this difference is the small body mass to volume of respired air as it's discussed by Chan & Meek (1994).

Just et al. (2010) found DEP and DBP in all 168 air samples from pregnant women at their third trimester in New York City, with geometric mean 1816 ng/m^3 and 459 ng/m^3 respectively. Air concentration of DEP was statistically correlated with urinary metabolite concentration MEP ($r=0.36$, $p<0.001$).

Øie et al. (1997) explored DEHP concentration in air and dust by recruiting 3754 children from 372 dwellings in Norway. Vacuumed dust samples and air particulate samples were collected, and Øie et al. (1997) found DEHP to be accounted for approximately 69% of the total amount of phthalates in total dust. Similar studies have been done in recent years, and the concentrations of DEHP have been increasing drastically, which is consistent with the increased production levels. Kanazawa et al. (2009) examined air and dust samples that were collected from 41 dwellings in Japan, and DEHP had the highest concentration of all tested phthalates in surface dust (220 – 10200 mg/kg), and floor dust (98.2 – 5850 mg/kg).

School is another indoor environment where children spend long periods of time. School and home environments in North Carolina were examined by Wilson et al. (2003), and indoor and outdoor air samples were collected from subjects' homes and their day-care centers. The mean indoor daycare concentration for indoor DBP was 488 ng/m3 whereas the indoor mean daycare concentration for BBP was 144 ng/m3 – their respective mean outdoor concentrations were: 73.9 ng/m3 and 133.9 ng/m3. Higher indoor phthalate concentrations in both air and dust suggest a contribution from indoor sources.

There is also evidence of a difference between night time and day time phthalate concentrations. The California Air Resources Board (CARB) (1992) found that night-time phthalates air concentrations were lower compared with daytime: DEP (320ng/m3 vs. 340 ng/m3); DBP (410 ng/m3 vs.460 ng/m3); BBzP (30 ng/m3 vs. 36 ng/m3); and DEHP (91 ng/m3 vs.110 ng/m3) (CARB, 1992). This may be due to the less cosmetics and household product usage during night time.

1.3 Health Effects

1.3.1 Toxicity in human infants and children

Several epidemiological studies have studied the association between phthalate exposure and adverse health outcomes in infants and children. Since phthalates can cross the placenta, exposure to the developing fetus during critical points in the development is also a concern (Mose et al., 2007).

In a multi-centre cohort study, Swan et al. (2005) reported that urinary MEP, MBP, MBzP, MiBP phthalate metabolite concentrations were negatively correlated with the anogenital index, the distance between anus and the genitalia, which may be an indicator of reproductive hazards. Swan et al. (2005) found the boys whose prenatal MBP concentration was at the upper 25^{th} percentile had a 10.2 times (95% CI: 2.5 – 42.2) greater chance to have a shorter than expected anogenital index.

The relationships between phthalate metabolites and children's neurodevelopment have also been studied (Engel et al., 2010; Cho et al., 2010; Kim et al., 2009). Cho et al. (2010) studied 667 Korean elementary school children, and found significant negative correlations between urinary MEHP phthalate concentration and Wechsler Intelligence Scale for Children's vocabulary score among boys. After adjusting for maternal IQ, there was also a significant negative correlation between children's vocabulary sub scores and urinary phthalate metabolite concentrations for parent compounds DEHP and DBP. (Cho et al., 2010)

A yet to be replicated Korean study examined the relationship between ADHD symptoms in children and their exposures to phthalates. Kim et al. (2009) analyzed urine samples collected from 261 Korean children 8 to 11 years old. After taking possible confounders into consideration (age, gender, IQ, parental education level, and socioeconomic status), Kim et al. (2009) found a positive correlation between phthalate urinary metabolite concentration and teacher-rated ADHD symptoms score.

In Finland, a cross-sectional study conducted by Jaakkola et al. (2000) examined exposure to phthalates and respiratory problems. Jaakkola et al. (2000) studied 2568 Finnish children age ranged from 1 to 7 years old, and lower respiratory tract symptoms were found to be strongly correlated with the presence of plastic wall materials. Symptoms included cough (OR=2.41, 95% CI: 1.04-5.63) and phlegm (OR=2.76, 95% CI: 1.03-7.41). Jaakkola et al. (2004) also examined a Russian cohort with 5951 school children from 8 to 12 years old. A significant correlation was found between the installation of linoleum flooring during the previous 12 months and both wheezing (OR=1.36; 95% CI: 1.00-1.86) and allergy (OR=1.31; 95% CI: 1.05-1.65) (Jaakkola et al., 2004).

Similar relationships were found by Kolarik et al. (2008); a Bulgaria cross-sectional study examined 102 children ranging in age from 2 to 7 years old who have respiratory symptoms, such as wheezing, rhinitis, and/or eczema. Kolarik et al. (2008) also included 82 non-symptomatic control children in the study. Kolarik et al. (2008) found significant correlations between wheezing in the preceding 12 months and DEHP phthalate concentration in settled household dust (p=0.035).

1.3.2 Toxicity in human adults

Several occupational asthma cases have shown a correlation with occupational exposure to heated mixtures of PVC in artificial leather and bottle caps production facilities (Lee et al., 1989) and residential fire fumes (Moisan et al., 1991).

In light of findings noted above regarding AGD, scientists have hypothesized that exposure to phthalates can lead to hormone disturbance, and eventually result in male infertility.

Huang et al. (2011) explored the relationship between DEHP concentration in personal air collected from 45 male workers in polyvinyl chloride plants in Taiwan. After adjusting for confounding factors, Huang et al. (2011) found that a 10-fold increase in personal air concentration of DEHP was associated with a 2.3-folds decrease in sperm motility (p=0.044). Similarly, Duty et al. (2005) explored the correlations between exposure to phthalates and hormone levels in adult men. They found that an inter-quartile range change in MBzP exposure was associated with a 10% (95% CI: -16, -4) decrease in follicle stimulating hormone concentrations, which is the hormone that regulates the reproductive process of the body. Jonsson et al. (2005) examined urine, serum and semen samples that were collected from 234 Swedish men; subjects within the highest quartile for MEP had fewer motile sperm (mean difference = 8.8%; 95% CI: 0.8-17), more immotile sperms (mean difference = 8.9%; 95% CI: 0.3-18).

1.4 Aim and objectives

The main aim of this analysis is to identify the determinants of phthalate exposure in Canadian children at approximately three months of age, by considering a large number of possible exposure sources.

In addition, a secondary aim was to study whether parents' socio-economic status such as income, occupation affects the level of exposure in children at three months of age.

2. Materials and Methods

2.1 Data sources

The data were obtained from the Canadian Healthy Infant Longitudinal Development (CHILD) study. The CHILD study is a multicentre, multidisciplinary, longitudinal, population-based birth cohort study of 5,000 children enrolled "pre-birth" and followed for five years (CHILD, 2007). This birth cohort is studying determinants of asthma and allergy in early life.

2.2 Study population and design

2.2.1 Study subjects

Subjects included in this analysis (N=578) were recruited prenatally for the CHILD Study from our four study centres in Vancouver, Edmonton, Winnipeg, and Toronto. The study protocols were reviewed by multiple research ethics boards including Simon Fraser University, University of British Columbia, University of Alberta, University of Manitoba, University of Toronto, and the appropriate hospitals at each centre. After receiving written and oral information about the study, subjects gave their informed consent before participating.

2.2.2 Study design and sample collections

On the day of each subject's home visit, when subjects were approximately three months of age, a single spot urine sample was collected by a trained field technician. The technician placed a sheet of Tegaderm film into a clean diaper on the baby's wetting area to prevent urine from being absorbed by the diaper (Figure 2.1). Four cotton pads were placed on the top of the Tegaderm, which were retrieved at the end of the home visit, and placed in a 60ml syringe. In the home, urine samples were aliquoted into six cryovials and transported back to the study centre in a cooler. Samples from four sites were sent to AXYS Technologies Inc. (Sidney, British Columbia) for analysis.

Figure 2.1 Tegaderm film on a cle   an diaper

Phthalate metabolites from five common parent compounds were analyzed. By analyzing biologically active metabolites instead of the parent compounds, we avoided potential laboratory contaminations. Seven phthalate metabolites were measured. The analysis entails the enzymatic deconjugation of the phthalate metabolites from their glucuronidated form to the monoester. Analysts were blinded to all subjects identifying information. Urine phthalate metabolite concentrations were adjusted for urine concentration by specific gravity (SG) using the following formula (Duty et al., 2003, Hauser et al., 2004, & Meek et al., 2009):

$$Pc = P\,[(1.0051 - 1) / (SG - 1)]$$

Where Pc is the SG adjusted phthalate metabolite concentration (ng/ml), P is the observed phthalate metabolite concentration (analyzed by AXYS), 1.0051 is the SG average of this cohort (N=578) and SG is the specific gravity of the individual urine sample, which was measured using a handheld refractometer.

2.2.3 Questionnaires

An important goal of CHILD is to obtain multiple objective measurements with emphasis focusing on the indoor environment (questionnaire, home inspection, dust collection), child responses (immune function, endocrine, pulmonary function, infections, allergies and clinical assessment) and genetic factors, together with extensive questionnaire data (demographics, family history, diet, activity, housing environment, psychosocial environment and stress). The questionnaires that were included for this analysis were listed in Table 2.1.

Table 2.1 List of questionnaires included

Questionnaires	Format	Time of administration
Home Environment	Completed by caregiver	3 Months of age
Home Environment RA Assessment	Completed by trained technician	3 Months of age
Child's Medication	Completed by caregiver	3 Months of age
Child's Nutrition	Completed by caregiver	3 Months of age
Socioeconomic Status (household income only)	Completed by caregiver	During 18 weeks of pregnancy

More details on each questionnaire are provided in Appendix table 2.

2.3 Data analysis

Univariate analyses were conducted to explore the distribution, central tendency and outliers for each phthalate metabolite. The distributions of these metabolites were extremely skewed; metabolite concentrations were then log10-transformed to achieve the normality assumption for multiple regression.

All questions in these five questionnaires were considered as potential independent variables for the multiple regression analysis. In order to identify the initial group of independent variables from more than 600 potential variables, we excluded independent variables that have more than 90% of missing data, and the ones with no or very little variation in the data (e.g. >98% had the same answers). By using univariate analysis, we explored attributes for all potential independent variables one at a time, all potential independent variables were categorized in to either binary, or ordinal variables. For overlapping questions between the home environment (answered by caregiver) and home environment RA assessment (answered by trained technician), only those were answered by trained technician were included in the analysis. Since we have overlapping data between these two questionnaires, an agreement study could be done to compare the data collected by the caregiver and the trained technicians. For this analysis we didn’t include any sub-questions in the questionnaires.

In order to gain some insight on which potential exposure factor is marginally associated with each of the metabolite concentrations when not taking any other exposures into account, bivariate analyses were conducted. For those ordinal independent variables that were defined previously, Pearson Correlation was used; whereas for binary independent variables, two sample t-tests were conducted to identify whether the average metabolite concentrations are different between the two groups of the subjects classified according to that binary independent variable and in what way they are different.

As with many other studies of low-level environmental chemicals, phthalate metabolite concentrations near the laboratory’s limits of quantification were often an issue. These concentrations cannot be precisely measured and are said to be below the detection limit (DL). Various methods have been used to deal with values between the DL. For practical purpose, the measurements that are subjected to DL are sometimes simply excluded from the analysis, or substituted with a constant equal to the detection limit or half the detection limit or the detection limit divided by square root of 2. These naïve methods have been adopted by many studies (Rudel et al., 2011; Yan et al., 2009; and Peck et al., 2006), however Smith et al. (2006) indicated these methods can potentially violate assumptions and lead to substantial biases when the concentrations are used as dependent variables in multiple regression model; since these methods are designed for cohort with few samples below the detection limits.

Alternatively, the measurement of metabolite concentration can be treated as left-censored when the actual value lies between zero and the limit of detection. The Tobit models (Tobin, 1958), also known as censored normal regression models, have been proposed to account for the left-censoring while describing the relationship between the dependent variable and the independent variables. This class of models assume a normal distribution for the dependent variable and the parameter estimate are obtained based on maximum likelihood method.

Tobit censored regression technique can perform quite well for samples has less than 30% of non-detectable (Uh et al., 2008). However, the R-squared values often used in the multiple linear regression models as a measure of goodness of fit cannot be produced in Tobit models. To evaluate how well the Tobit model fits, one method is to compare the predicted outcome values based on Tobit model to the observed outcome values in the data set. The correlation between the predicted and observed values is then calculated and squared to produce a measure called multiple squared correlations. This measure is analogous to the R-squares values in the sense that if it takes a value of 0.50, it implies that the predicted values of metabolite concentration obtained from the fitted Tobit model share about the 50% of their variance with observed metabolite concentration. There are some other modified version of R-squares been proposed such as McFadden's R-square, Cox-Snell R-square and McKelvey & Zavoina's R-square. Akaike information criterion (AIC), BIC and log likelihood ratios can also been used to assess the goodness of fit when comparing competing Tobit models. For this analysis, we only looked into the AIC numbers between different selection steps, however we didn't use other methods listed above to assess the goodness of the fit of the model due to time restrictions.

As displayed in the (Table 3.2) there were only two subjects whose MBP phthalate metabolite concentrations were below the detection limit, we applied the standard multiple regression method by removing those two subjects that were below their detection limits. Forward, backward and stepwise model selection methods with both 0.10 and 0.05 significant levels were used to select the final fitted model.

We also investigated the impact of SES on the phthalate metabolite concentrations; in this case we used household income as the indicator of the SES. Household income was included as one of the explanatory variables when we try to identify the determinants of phthalate exposure. We also did stratified analysis for each metabolite by fitting the final selected model on the data stratified by the average household income for each city.

3. Chapter 3: Results

3.1 Summary Statistics

3.1.1 Subject demographics

Of 578 subjects who provided urine samples, more samples were from western centres (Vancouver, 35.09%; Edmonton, 17.55%; total 52.64%) than eastern centers (Winnipeg, 31.52%; Toronto 14.31%; total 45.83%). (Table3.1)

Table 3.1 Demographic distributions (N=578)

Centers	*# of Urine samples*	*Percentage*	*Total*
Vancouver	206	35.09%	52.64%
Edmonton	103	17.55%	
Winnipeg	185	31.52%	45.83%
Toronto	84	14.31%	

3.1.2 Urinary phthalate metabolites

There is a moderate to high percentage of missing data (Table 3.2) for most phthalate metabolites MEP, MBP, MBzP, MEHHP and MEOHP (approximately < 30%) and MEHP (approximately 50%). Since only 19.03% of MMP phthalate metabolite concentrations were above the detection limit, there will not be enough power to detect the effects of all the exposure factors. Taking this into consideration, MMP was not considered for analysis. There are some extremely large metabolite concentration values observed for MBP (716 ng/ml), MBzP (205 ng/ml), and MEP (1960 ng/ml). These observations may have strong influence on the analysis and may play a role on some of the un-expected negative associations we found in this analysis.

Table 3.2 Phthalate metabolites (ng/ml) distributions (N is above DL)

Metabolites	N	Mean	Std Dev	Minimum	Maximum	25th Percentile	75th Percentile	Above DL
MMP	110	6.27	7.75	1.04	40.8	2.04	6.07	19.03%*
MBP	576	29.85	54.54	2.15	716	10.20	32.30	99.65%
MBzP	419	5.94	12.68	1	205	1.41	5.34	72.49%
MEP	510	27.69	104.74	1.24	1960	5.05	17.30	88.24%
MEHP	297	3.45	4.63	0.98	36.4	1.41	3.56	51.38%
MEHHP	442	4.7	5.4	1	43.6	1.76	5.00	76.47%
MEOHP	399	3.61	3.77	1	30.7	1.53	3.96	69.03%

3.2 Bivariate analysis

Appendix Table 1 shows the results from the bivariate analysis, identifying the strength of marginal association between dependent variable (urinary phthalate metabolites) and independent variable individually at 0.05 significant levels. We found store (MBP, MEHP) or heat food (MBP) in hard plastics were significantly associated with their urinary metabolite concentration (p = 0.002, p = 0.004 and p = 0.008 respectively). Similar to the plastic exposure noted earlier, we found the usage of plastic bowl is significantly associated with MEHP (p=0.004), MEOHP (p=0.033) and MBP (p=0.019). We also found household income to be marginally negatively associated with MBP (p=0.038).

Bathroom leaking and moisture were found significantly associated with several phthalate metabolites: MBP (p=0.013), MEP (p=0.012) and MEOHP (p=0.006). We also explored leaking and moisture in other rooms such as kitchen, bedroom, living room, and kitchen, however none of them were significant at 0.05 significant level.

Similar to several other studies, we found MEP significantly associated with baby powder (p=0.000), other skin product (p=0.021), spray air fresheners (p=0.007), dusting polisher (p=0.021), unscented and scented candle (p=0.033 & 0.008), incense (p=0.003) and bathroom tile cleaner (p=0.002). More detailed information can be found in the appendix table 2.

3.3 Multiple Regression Analysis

3.3.1 Multiple regression model – MBP phthalate metabolite

In multiple regression analysis of MBP phthalate metabolite concentration, we identified several potential exposure sources at age of 3 months old (Table 3.3.1). Subjects who stored breast milk, formula, food or other drinks in hard plastic containers to those who do not, MBP phthalate metabolite concentration increased by 38% (P<.0001). We found evidence of leaks in the bathroom (MBP increases by 28%, p=0.0004), working with hazardous materials (MBP increases by 30%, p=0.005), older floor in mother's bedroom (MBP increases by 7%, p=0.031), and also each additional number of solvent in use or presence (MBP increases by 12%, p=0.001) significantly associated with MBP metabolite concentration. Negative correlations were also found between MBP metabolite concentration and play with or use soft plastic toys / teething rings that involves putting them in his / her mouth (MBP decreases by 18%, p=0.006), each additional number of multi-surface cleaner in use or presence (MBP decreases by 5%, p=0.024), and each additional level of hard plastic bottle usage frequency (MBP decreases by 6%, p=0.033). For the negative correlation between play with or use soft plastic toys / teething rings that involves putting them in his / her mouth and MBP metabolite concentration may be due to the two subjects with the highest MBP metabolite concentrations do not use them. Approximately 10% of the variations in MBP concentration can be explained by this model.

Since there are two subjects with greater than 700ng/ml urinary MBP phthalate metabolite, we looked into their contributions by removed them and ran the standard multiple regression, they increased the overall variance by 5% (R2=0.15), the direction and strength of association were similar to the model with these two subjects included (Table 3.3.1).

Feed baby with hard plastic bottle or sippy cup had the highest partial R-square (0.098), which is its marginal contribution to the variation of MBP when all other variables are already included in the model. There were five explanatory variables that were highly significant (p<=0.01), and they have similar partial R-square value between 1% to 3% contributions.

Table 3.3.1 MBP and potential exposure sources (N=550), R-Squared = 0.10

Variables	Type	% of Exposed	Backward (R2 = 0.10)		
			Parameter Estimate	Partial R-square	Pr > F
Do you STORE breast milk, formula, food or other drinks in Hard plastic?	Binary	25.20%	38%	0.017	<.0001
Is there any evidence of LEAKS in the bathroom, baby uses?	Binary	7.80%	28%	0.025	0.0004
Solvent in use & Presence	Ordinal	56.10%	12%	0.011	0.001
Household member who work with hazardous materials on the job?	Binary	15.10%	30%	0.011	0.005
Play with or use soft plastic toys/teething rings that involves putting them in his/her mouth?	Binary	37.30%	-18%	0.011	0.006
Multi-surface cleaner in use & Presence	Ordinal	93.70%	-5%	0.009	0.024
How often did you feed baby with the Hard plastic bottle/Sippy cup?	Ordinal	16.80%	-6%	0.098	0.033
Age of floor - Mother's bedroom	Ordinal	70.50%	7%	0.007	0.031

We also compared the results from three different selection methods, backward, forward, and stepwise selections, they all produce relative the same results and with the same direction of association as displayed in Table 3.3. This confirms that validity and robustness of the analysis.

Table 3.3.1a MBP stratification analysis (Household income above average vs. below average)

	Stratified Analysis Household income > = Average		Stratified Analysis Household income < Average		Overall Analysis	
Variables	Effect Estimate	P-Value	Effect Estimate	P-Value	Effect Estimate	P-Value
Do you STORE breast milk, formula, food or other drinks in Hard plastic?	38%	0.003	41%	0.00	38%	<.0001
Is there any evidence of LEAKS in the bathroom, baby uses?	33%	0.002	26%	0.03	28%	0.0004
Solvent in use & Presence	15%	0.002	7%	0.21	12%	0.001
Household member who work with hazardous materials on the job?	67%	0.000	2%	0.89	30%	0.005
Play with or use soft plastic toys/teething rings that involves putting them in his/her mouth?	-12%	0.172	-22%	0.01	-18%	0.006

Multi-surface cleaner in use & Presence	-6%	0.078	-3%	0.37	-5%	0.024
How often did you feed baby with the Hard plastic bottle/Sippy cup?	-6%	0.100	-6%	0.13	-6%	0.033
Age of floor - Mother's bedroom	0%	0.033	0%	0.79	7%	0.031

To get some insight on the effect of SES on the metabolite concentration, we then fit the final MBP model (Table 3.3.1) on the data stratified by household income. For subjects whose household income above average, play with or use soft plastic toys/teething rings (p=0.172), Multi-surface cleaner in use and presence (p=0.078) and frequency of feeding baby with the hard plastic bottles (p=0.1) were no longer significant. Whereas for subjects' household income less than average, there were only three variables (Hard plastic as storage, evidence of leaks in bathroom – baby uses, and play or use soft plastic toys/teething rings) still significantly associate with urinary MBP phthalate metabolite concentrations. However, solvent in use & presence, household member who work with hazardous materials on the job are not significant any more.

3.3.2 Tobit regression model – MBzP phthalate metabolite

For urinary MBzP phthalate metabolite concentrations, 158 subjects (out of 578) had concentrations that were below the limit of detection.

Table 3.3.2 reports the exposure sources that were found to be associated with urine phthalate metabolite MBzP concentrations in the final regression models. In our results, holding all other exposure sources constant, subjects who had soft vinyl flooring in kitchen had 35.7% (P<.0001) higher urinary MBzP concentration than those who do not have soft vinyl flooring in their kitchen.

We found that MBzP metabolite concentrations were highly significantly associated with having soft vinyl tiles in the kitchen (MBzP increases by 50.83%, p<0.0001), household member works with hazardous material on the job (MBzP increases by 43.65%, p=0.004), having and use floor cleaners (MBzP increases by 12.07%, p=0.004) and store breast milk, formula, or food in soft plastic (MBzP increases by 23.08%, p=0.032).

Negative correlations that contradict to other studies were found between having and use glass cleaner (MBzP decreases by 9.41%, p=0.005), having plastic toys in the living room (MBzP decreases by 13.84%, p=0.013), having plastic playmats in the living room (MBzP decreases by 17.40%, p=0.024) and urinary MBzP phthalate metabolite concentrations. We also found that for the child who is sleeping alone compared to those who do not, MBzP metabolite concentration decreased by 33.09% (p<0.0001). This may be due to less exposure through parents personal care products on transferred from skin.

Table 3.3.2 MBzP and potential exposure sources (N=578)

Tobit Model (MBzP) P=0.10							
Variables	**Type**	**% of Exposed**	**Parameter Estimate**	**Standard Error**	**95% Confidence Limits**		**Pr > ChiSq**
Is the child sleeping alone in this bedroom?	Binary	58.8%	-33.09%	0.042	0.257	-0.092	<.0001
Soft vinyl (tiles/sheet) - Kitchen	Binary	35.7%	50.83%	0.044	0.093	0.265	<.0001
Household member who work with hazardous materials on the job?	Binary	17.4%	43.65%	0.054	0.051	0.264	0.004
Floor Cleaner in use & Presence	Ordinal	61.2%	12.07%	0.017	0.016	0.083	0.004
Glass cleaner in use & Presence	Ordinal	85%	-9.41%	0.015	-0.073	-0.013	0.005
Plastic toys - Living room, baby slept	Binary	96.7%	-13.84%	0.026	0.014	0.116	0.013
Plastic/foam floor playmats: - Living room, baby slept	Binary	88.1%	-17.40%	0.037	-0.155	-0.011	0.024
Did you breastfeed baby for any duration (more than a few days) since birth?	Binary	93.6%	-34.07%	0.084	-0.345	-0.017	0.031
Do you STORE breast milk, formula, food or other drinks in Soft plastic (e.g., bottle liners, bags)?	Binary	38.1%	23.08%	0.042	0.008	0.173	0.032
Age of floor - Living room, baby slept	Ordinal	.	0.16%	0	0	0.001	0.043
Hard vinyl (tiles) - Kitchen	Binary	6.7%	0.04%	0.081	0.003	0.319	0.046
Bathroom tile cleaner in use & Presence	Ordinal	65.5%	6.95%	0.015	0	0.059	0.05
Have you brought any major pieces of NEW furniture into your home since you completed the Home environment Questionnaire during your pregnancy?	Binary	45.5%	-15.63%	0.04	-0.152	0.005	0.065

Use pacifier	Binary	57.1%	-15.76%	0.041	-0.155	0.006	0.07
Multi-surface cleaner in use & Presence	Ordinal	92.6%	-5.53%	0.015	-0.054	0.004	0.097
Scented laundry detergent in use & Presence	Ordinal	86.2%	-4.32%	0.012	-0.042	0.004	0.099

After stratified by household income, many variables that were originally significant in the Tobit analysis on the whole data were no long significant (see Table 3.3.2a). Specifically, child sleeping alone, softy vinyl in kitchen, floor cleaner, glass cleaner, plastic/foam playmats, breastfeeding and store milk and food in plastic containers were found unrelated to MBzP concentration for either above or below average income groups. Household member who work with hazardous material remained to be positively associated with MBzP only for above average income group but not for below average income group. Age of flooring in living room, hard vinyl floor in kitchen and bathroom tile cleaner remained positively correlated to MBzP only for below average group but not above average group. Plastic toy in living room was negatively associated with MBzP in the overall analysis (decreased by 13.84%, p=0.013), but now became positively associated for below average group (increased by 25%, p=0.01) and had no association with MBzP for above average income group. Bought new furniture was not a significant exposure factor in the overall analysis, but now became negatively associated with MBzP for the above average income group. These results indicated that household income may play an important role on the urinary MBzP phthalate metabolite concentration.

Table 3.3.2a MBzP stratification analysis (Household income above average vs. below average)

	Stratified Analysis Household income > = Average		**Stratified Analysis Household income < Average**		**Overall Analysis**	
Variables	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**
Is the child sleeping alone in this bedroom?	-17%	0.15	-3%	0.84	-33.09%	<.0001
Soft vinyl (tiles/sheet) - Kitchen	15%	0.28	17%	0.22	50.83%	<.0001
Household member who work with hazardous materials on the job?	37%	0.06	10%	0.56	43.65%	0.004
Floor Cleaner in use & Presence	9%	0.11	7%	0.23	12.07%	0.004
Glass cleaner in use & Presence	-7%	0.14	-6%	0.18	-9.41%	0.005
Plastic toys - Living room, baby	7%	0.36	25%	0.01	-13.84%	0.013

slept						
Plastic/foam floor playmats: - Living room, baby slept	-11%	0.31	-13%	0.18	-17.40%	0.024
Did you breastfeed baby for any duration (more than a few days) since birth?	-3%	0.92	3%	0.91	-34.07%	0.031
Do you STORE breast milk, formula, food or other drinks in Soft plastic (e.g., bottle liners, bags)?	13%	0.34	9%	0.48	23.08%	0.032
Age of floor - Living room, baby slept	5%	0.36	0%	0.03	0.16%	0.043
Hard vinyl (tiles) - Kitchen	13%	0.73	73%	0.01	0.04%	0.046
Bathroom tile cleaner in use & Presence	1%	0.78	15%	0.00	6.95%	0.05
Have you brought any major pieces of NEW furniture into your home since you completed the Home environment Questionnaire during your pregnancy?	-35%	0.00	-8%	0.51	-15.63%	0.065
Use pacifier	0%	0.99	-19%	0.10	-15.76%	0.07
	Stratified Analysis Household income > = Average		**Stratified Analysis Household income < Average**		**Overall Analysis**	
Variables	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**
Multi-surface cleaner in use & Presence	-1%	0.79	-6%	0.17	-5.53%	0.097
Scented laundry detergent in use & Presence	-2%	0.55	-7%	0.06	-4.32%	0.099

3.3.3 Tobit regression model – MEP phthalate metabolite

For urinary MEP phthalate metabolite concentrations, there were 67 subjects' concentrations that were left censored values.

The exposure sources found to be associated with urine phthalate metabolite MEP concentrations in the final regression models are reported in Table 3.5. In our results, holding all other exposures in the final model constant, subjects who use baby powder frequency increases, their MEP concentration increases by 31.16% (p=0.0004).

We found having and use air fresheners (MEP increase by 14.08%, p=0.0010), use other skin product (MEP increases by 18.41%, p=0.0159) and having / using dusting polish (MEP increases by 12.02%, p=0.0203) to be significantly associated with MEP metabolite concentration. Having a basement (MEP decreases by 23.97%, p=0.0133) was found to be negatively associated with MEP metabolite concentration.

Table 3.3.3 MEP and potential exposure sources (N=577)

Tobit Model (MEP) 0.1							
Variables	**% of Exposed**	**Type**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Pr > ChiSq**
Baby powder, talc or cornstarch:	17.50%	Ordinal	31.16%	0.0334	0.0524	0.1833	0.0004
Air fresheners in use & presence	20.60%	Ordinal	14.08%	0.0174	0.0230	0.0914	0.0010
Age of floor - child's bedroom	24.70%	Ordinal	0.04%	0.0001	0.0001	0.0003	0.0014
Does the home have a basement?	69.20%	Binary	-23.97%	0.0481	-0.2133	-0.0248	0.0133
Other skin products	21.40%	Ordinal	18.41%	0.0301	0.0138	0.1331	0.0159
Dusting polish or spray in use & presence	27.80%	Ordinal	12.02%	0.0213	0.0077	0.0910	0.0203
Bathroom tile cleaner in use & presence	66.10%	Ordinal	7.47%	0.0159	0.0002	0.0625	0.0486
Hand dishwashing detergent in use & presence	99.60%	Ordinal	-12.12%	0.0286	-0.1122	0.0000	0.0500
Tobit Model (MEP) 0.1							
Variables	**% of Exposed**	**Type**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Pr > ChiSq**
Multi-surface cleaner in use & presence	94.10%	Ordinal	-6.80%	0.0158	-0.0615	0.0003	0.0521
Plastic toys - Mother's bedroom	27.80%	Ordinal	-15.26%	0.0399	-0.1500	0.0062	0.0712
Solvent in use & presence	57.50%	Ordinal	9.62%	0.0226	-0.0045	0.0842	0.0784
Play with or use soft plastic toys/teething rings that involves putting them in his/her mouth?	36.70%	Binary	-16.21%	0.0448	-0.1645	0.0109	0.0861
Scented candle in use & presence	54.30%	Ordinal	7.32%	0.0182	-0.0049	0.0663	0.0909

The final MEP model was then stratified by household income (Table 3.3.3a). Several variables remained significant in the same direction as in the overall analysis but only in below average income group, or in above average income group. For subjects who are in the below the average household income group, using baby powder, home has a basement, dusting polish in use & presence, and hand dishwashing detergent in use & presence were still significantly associated with urinary MEP phthalate metabolite concentration, with same directions as their overall analysis result. For subjects who are in the above average household income group, age of floor in child’s bedroom, and bathroom tile cleaner in use & presence were still significantly associated with urinary MEP phthalate metabolite concentration, with same directions as their overall analysis result.

Plastic toys in mother’s bedroom (MEP decrease by 15.26%, p=0.0712) was not significant in the overall analysis but became negatively associated with MEP in the above average group (MEP decrease by 34%, p<0.01). Only air fresheners in use & presence were still significant associated with urinary MEP phthalate metabolite concentration in both above and below the average household income groups, with same direction of associations as their overall Tobit result.

Table 3.3.3a MEP stratification analysis (Household income above average vs. below average)

	Stratified Analysis Household income > = Average		Stratified Analysis Household income < Average		Tobit results	
Variables	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**
Baby powder, talc or cornstarch:	20%	0.08	26%	0.01	31.16%	0.0004
Air fresheners in use & presence	12%	0.02	14%	0.01	14.08%	0.001
Age of floor - child's bedroom	0%	0.00	0%	0.16	0.04%	0.0014
Does the home have a basement?	-3%	0.82	-27%	0.02	-23.97%	0.0133
	Stratified Analysis Household income > = Average		**Stratified Analysis Household income < Average**		**Tobit results**	
Variables	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**
Other skin products	16%	0.13	10%	0.23	18.41%	0.0159
Dusting polish or spray in use & presence	3%	0.60	25%	0.00	12.02%	0.0203
Bathroom tile cleaner in use & presence	10%	0.03	3%	0.48	7.47%	0.0486
Hand dishwashing detergent in use & presence	7%	0.43	-14%	0.04	-12.12%	0.05
Multi-surface cleaner in use & presence	-8%	0.11	-8%	0.05	-6.80%	0.0521
Plastic toys - Mother's bedroom	-34%	0.00	-3%	0.80	-15.26%	0.0712
Solvent in use & presence	10%	0.14	-2%	0.72	9.62%	0.0784
Play with or use soft plastic toys/teething rings that involves putting them in his/her mouth?	-15%	0.24	-18%	0.13	-16.21%	0.0861
Scented candle in use & presence	5%	0.34	4%	0.46	7.32%	0.0909

3.3.4 Tobit regression model – MEHP phthalate metabolite

For urinary MEHP phthalate metabolite concentrations, there were 279 subjects' concentrations that were left censored values.

DEHP is the parent compound for MEHP, MEHHP, and MEOHP, and is presently the most common phthalate found in plastic. DEHP can also be used as an emulsifier in food and the food industry in Taiwan has been adding DEHP to sport drinks and fruit juices to give them the cloudy look. (CFIA, 2011) Our results also indicated these potential sources: hard plastic containers, drain cleaner, bathroom cleaner, hand washing detergent, and plastic toys. For example, hold all the other potential exposure sources in the final model constant, the urinary MEHP phthalate metabolite concentrations for subjects who store breast milk, formula, food or other drinks in hard plastic were 48.01% (p=0.0008) higher than those who do not store food in hard plastics.

Having and using drain cleaner (MEHP increases by 19.78%, p=0.0136), solvent (MEHP increases by 13.74%, p=0.0159), as well as increasing the total number of the products (MEHP increases by 15.11%, p= 0.0289) were found positively associated with MEHP metabolite concentrations.

There are several negative associations that contradict to other studies, subjects who has laminate flooring in the kitchen (MEHP decrease by 38.43%, p=0.005), with evidence of leak in bathroom (MEHP decreases by 26.58%, p=0.0209) or people who takes capsule medication (MEHP decreases by 24.49%, p=0.0212) have lower MEHP metabolite concentrations.

Table 3.3.4 MEHP and potential exposure sources (N=576)

Tobit Model (MEHP) 0.10							
Variable	**Type**	**% of Exposed**	**Parameter Estimate**	**Standard Error**	**95% Confidence Limits**		**Pr > ChiSq**
Is there a child's bedroom or a bedroom that will become the child's bedroom?	Binary	83.8%	81.09%	0.0629	0.1347	0.3812	<.0001
do you STORE breast milk, formula, food or other drinks in Hard plastic?	Binary	31%	48.01%	0.051	0.0704	0.2703	0.0008
Plastic toys - Living room, baby slept?	Binary	96.6%	-19.16%	0.0283	-0.148	-0.037	0.0011

Did you breastfeed baby for any duration (more than a few days) since birth?	Binary	92.3%	-49.52%	0.0957	-0.484	-0.109	0.0019
how often did you feed baby with the Glass bottle?	Ordinal	31%	-13.74%	0.0227	-0.109	-0.02	0.0047
Laminate -Kitchen	Binary	10.4%	-38.43%	0.075	-0.358	-0.064	0.005
Liquid or solid air freshener in use & presence	Ordinal	24.9%	-10.55%	0.0182	-0.084	-0.013	0.0079
Is there any MOULD in the bathroom baby use?	Binary	88.6%	34.52%	0.0491	0.0326	0.225	0.0087
Drain cleaner in use & presence	Ordinal	46.1%	19.78%	0.0318	0.0161	0.1407	0.0136
scented laundry detergent in use & presence	Ordinal	83.5%	-7.49%	0.0137	-0.061	-0.007	0.0137
solvent in use & presence	Ordinal	61.3%	13.74%	0.0232	0.0105	0.1013	0.0159
Is there any evidence of LEAKS in the bathroom, baby use?	Binary	84.2%	-26.58%	0.0581	-0.248	-0.02	0.0209
Medication Exposure	Binary	22.9%	-24.49%	0.053	-0.226	-0.018	0.0212
Laminate - Child's bedroom	Binary	10.1%	-32.00%	0.0759	-0.316	-0.019	0.0272
Total number of cleaning agents observed:	Ordinal	98.3%	15.11%	0.028	0.0063	0.1159	0.0289
Household income	Binary	51.5%	-21.00%	0.0483	-0.197	-0.008	0.0339
how often did you feed baby with the Bottle with soft plastic bottle liner?	Ordinal	15.5%	-12.48%	0.0285	-0.114	-0.002	0.0423
hand dishwashing detergent in use & presence	Ordinal	100%	17.52%	0.0349	0.0018	0.1384	0.0443

Tobit Model (MEHP) 0.10							
Variable	**Type**	**% of Exposed**	**Parameter Estimate**	**Standard Error**	**95% Confidence Limits**		**Pr > ChiSq**
how often did you feed baby with the Nursing with nipple shields?	Ordinal	14.8%	15.08%	0.0324	-0.002	0.1245	0.0593
Are you using disposable diapers on baby?	Binary	93.6%	-34.13%	0.0973	-0.372	0.0094	0.0624
Baby wipes	Binary	94.3%	11.58%	0.0279	-0.007	0.1022	0.0879

To get some insight on the effect of SES on the metabolite concentration, we then fit the final MEHP model (Table 3.3.4a) on the data stratified by household income. After we stratified by household income, majority of the explanatory variables (15 out of 21) that were significant in the overall Tobit result, were no longer significant in the stratified groups. For child who has their own bedroom or they will have in the future (MEHP increase by 81.09%, p<0.0001) was significantly associated with only household income above average group (MEHP increase by 72%, p=0.04) after stratification. For the blow average household income group, store food in hard plastic (MEHP increase by 42%, p=0.04), feed with glass bottle (MEHP decrease by 16%, p=0.03), scented laundry detergent in use & presence (MEHP decrease by 12%, p=0.01) and bottle with soft plastic liner (MEHP decrease by 23%, p=0.02) were associated with urinary MEHP phthalate metabolite concentration significantly after stratification.

Table 3.3.4a MEHP stratification analysis (Household income above average vs. below average)

	Stratified Analysis Household income > = Average		Stratified Analysis Household income < Average		Tobit results	
Variables	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**
Is there a child's bedroom or a bedroom that will become the child's bedroom?	72%	0.04	36%	0.11	81.09%	<.0001
do you STORE breast milk, formula, food or other drinks in Hard plastic?	9%	0.56	42%	0.04	48.01%	0.0008
Plastic toys - Living room, baby slept?	-8%	0.34	-5%	0.64	-19.16%	0.0011
Did you breastfeed baby for any duration (more than a few days) since birth?	29%	0.39	-7%	0.84	-49.52%	0.0019
how often did you feed baby with the Glass bottle?	-6%	0.40	-16%	0.03	-13.74%	0.0047
Laminate -Kitchen	-37%	0.06	-36%	0.08	-38.43%	0.005
Liquid or solid air freshener in use & presence	4%	0.51	-11%	0.06	-10.55%	0.0079
	Stratified Analysis Household income > = Average		**Stratified Analysis Household income < Average**		**Tobit results**	
Variables	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**
Is there any MOULD in the bathroom baby use?	9%	0.59	16%	0.40	34.52%	0.0087
Drain cleaner in use & presence	3%	0.77	12%	0.31	19.78%	0.0136
scented laundry detergent in use & presence	-6%	0.13	-12%	0.01	-7.49%	0.0137
solvent in use & presence	13%	0.07	1%	0.91	13.74%	0.0159
Is there any evidence of LEAKS in the bathroom, baby use?	-23%	0.13	-18%	0.30	-26.58%	0.0209
Medication Exposure	7%	0.68	-24%	0.17	-24.49%	0.0212
Laminate - Child's bedroom	-1%	0.96	-9%	0.70	-32.00%	0.0272

Total number of cleaning agents observed:	0%	1.00	1%	0.89	15.11%	0.0289
Household income					-21.00%	0.0339
how often did you feed baby with the Bottle with soft plastic bottle liner?	-12%	0.12	-23%	0.02	-12.48%	0.0423
hand dishwashing detergent in use & presence	0%	0.95	-1%	0.84	17.52%	0.0443
how often did you feed baby with the Nursing with nipple shields?	4%	0.74	5%	0.58	15.08%	0.0593
Are you using disposable diapers on baby?	-29%	0.25	-30%	0.32	-34.13%	0.0624
Baby wipes	1%	0.88	-5%	0.58	11.58%	0.0879

3.3.5Tobit regression model – MEHHP phthalate metabolite

For MEHHP phthalate metabolite concentrations, there were 136 subjects' concentrations that were left censored values.

Table 3.7 reports the exposure sources that were found to be associated with urine phthalate metabolite MEHHP concentrations in the final regression model. Holding all the other potential exposure sources in our final model constant, subjects who store breast milk, formula, food or other drunks in hard plastic, their MEHHP phthalate metabolite concentration were 48.01% higher than those who do not store food in hard plastics.

We found mould in the bathroom (MEHHP increases by 34.52%, p=0.0087), usage of drain cleaner (MEHHP increases by 5.03%, p=0.0261), having and use hand dishwashing detergent (MEHHP increases by 17.52%, p=0.0443).

Several expected negative correlations were found. We found the negative correlation between household income and their MEHHP metabolite concentration, for those subjects whose household income were below the average of this cohort, their MEHHP metabolite concentration were 21.00% higher than those were above the average (p=0.0339); also for those subject who breast fed baby for any duration, their phthalate metabolite were 49.52% lower than those who were not breast fed (p=0.0019).

Table 3.3.5 MEHHP and potential exposure sources (N=578)

Tobit Model (MEHHP) 0.10

Variables	% of Exposed	Type	Estimate	Standard Error	95% Confidence Limits		Pr > ChiSq
Is there a child’s bedroom or a bedroom that will become the child’s bedroom?	0.794	Binary	0.8109	0.0629	0.1347	0.3812	<.0001
do you STORE breast milk, formula, food or other drinks in Hard plastic?	25.30%	Binary	48.01%	0.051	0.0704	0.2703	0.0008
Plastic toys - living room	97.30%	Binary	-19.16%	0.0283	-0.1478	-0.037	0.0011
Did you breastfeed baby for any duration (more than a few days) since birth?	93.20%	Binary	-49.52%	0.0957	-0.4844	-0.1094	0.0019
how often did you feed baby with the Glass bottle?	32.10%	Ordinal	-13.74%	0.0227	-0.1087	-0.0197	0.0047
Laminate - living room	12.40%	Binary	-38.43%	0.075	-0.3577	-0.0636	0.005
Liquid or solid air freshener in use & presence	30.30%	Ordinal	-10.55%	0.0182	-0.0841	-0.0127	0.0079
Is there any MOULD in the bathroom, baby uses?	89.80%	Binary	34.52%	0.0491	0.0326	0.225	0.0087
Drain cleaner in use & presence	38.90%	Ordinal	19.78%	0.0318	0.0161	0.1407	0.0136
scented laundry detergent in use & presence	83.70%	Ordinal	-7.49%	0.0137	-0.0607	-0.0069	0.0137
solvent in use & presence	56.60%	Ordinal	13.74%	0.0232	0.0105	0.1013	0.0159
Is there any evidence of LEAKS in the bathroom, baby uses?	85.50%	Binary	-26.58%	0.0581	-0.2482	-0.0203	0.0209
Medication Exposure	26.20%	Binary	-24.49%	0.053	-0.2258	-0.0182	0.0212
Laminate - child's bedroom	12.40%	Binary	-32.00%	0.0759	-0.3163	-0.0188	0.0272
Total number of cleaning agents observed	97.30%	Ordinal	15.11%	0.028	0.0063	0.1159	0.0289
Household income	48.90%	Binary	-21.00%	0.0483	-0.197	-0.0078	0.0339
how often did you feed baby with the Bottle with soft plastic bottle liner?	17.40%	Ordinal	-12.48%	0.0285	-0.1138	-0.002	0.0423
hand dishwashing detergent in use & presence	100.00%	Ordinal	17.52%	0.0349	0.0018	0.1384	0.0443

Tobit Model (MEHHP) 0.10

Variables	% of Exposed	Type	Estimate	Standard Error	95% Confidence Limits		Pr > ChiSq
How often did you feed baby with the Nursing with nipple shields?	13.10%	Ordinal	15.08%	0.0324	-0.0024	0.1245	0.0593
Are you using disposable diapers on baby?	93.70%	Binary	-34.13%	0.0973	-0.372	0.0094	0.0624
Baby wipes	93.70%	Binary	11.58%	0.0279	-0.0071	0.1022	0.0879

Table 3.3.5a MEHHP stratification analysis (Household income above average vs. below average)

	Stratified Analysis Household income > = Average		Stratified Analysis Household income < Average		Tobit results	
Variables	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**
Is there a child's bedroom or a bedroom that will become the child's bedroom?	-0.23	0.1264	-0.09	0.4354	0.8109	<.0001
Did you breastfeed baby for any duration (more than a few days) since birth?	-32%	0.0752	-20%	0.3531	-49.52%	0.00
Do you STORE breast milk, formula, food or other drinks in Hard plastic?	-1%	0.9615	37%	0.0129	48.01%	0.00
Plastic toys - living room	-7%	0.2605	3%	0.6926	-19.16%	0.00
How often did you feed baby with the Glass bottle?	-1%	0.8505	-5%	0.331	-13.74%	0.00
Laminate - living room	-19%	0.0699	-18%	0.0745	-38.43%	0.01
Liquid or solid air freshener in use & presence	0%	0.9642	11%	0.0093	-10.55%	0.01
Is there any MOULD in the bathroom, baby uses?	4%	0.732	25%	0.0447	34.52%	0.01
Drain cleaner in use & presence	5%	0.4715	12%	0.1847	19.78%	0.01
scented laundry detergent in use & presence	0%	0.9981	-8%	0.0265	-7.49%	0.01
solvent in use & presence	6%	0.278	10%	0.088	13.74%	0.02
Is there any evidence of LEAKS in the bathroom, baby uses?	6%	0.6121	17%	0.2333	-26.58%	0.02
Medication Exposure	-7%	0.4772	2%	0.8766	-24.49%	0.02
Laminate - child's bedroom	19%	0.3068	48%	0.0388	-32.00%	0.03
Total number of cleaning agents observed	6%	0.3013	0%	0.9932	15.11%	0.03
Household income	.	.	.	.	-21.00%	0.03
How often did you feed baby with the Bottle with soft plastic bottle liner?	2%	0.7331	0%	0.9747	-12.48%	0.04
Hand dishwashing detergent in use & presence	7%	0.4057	-11%	0.1203	17.52%	0.04

How often did you feed baby with the Nursing with nipple shields?	-6%	0.3404	3%	0.6726	15.08%	0.06
Are you using disposable diapers on baby?	-21%	0.3094	-20%	0.2889	-34.13%	0.06
Baby wipes	-1%	0.8147	4%	0.4873	11.58%	0.09

To get some insight on the effect of SES on the metabolite concentration, we then fit the final MEHHP model (Table 3.3.5a) on the data stratified by household income. More than half (13 out of 20) explanatory variables which were significantly associated with urinary MEHHP phthalate metabolite concentrations in the overall Tobit result were no longer significant after we stratified by household income. These include many variables (e.g. Bottle with soft plastic liners, plastic toys in living room, laminate flooring in living room) with un-expected significant negative associations with MEHHP in the overall analysis.

Liquid or solid air freshener in use & presence (MEHHP decrease by 10.55%, p=0.0079) and Laminate flooring in child's bedroom (MEHHP decrease by 32%, p=0.0272) had the significant un-expected negative associations with urinary MEHHP phthalate metabolite concentrations in the overall Tobit result, once we stratified by household income, both of them were found positively associated with urinary MEHHP phthalate metabolite concentration in the below household average income group (p=0.009 and 0.04 respectively).

Store food in hard plastic, scented laundry detergent use & presence, and mould in bathroom were found significantly associated with urinary MEHHP phthalate metabolite concentration in the overall Tobit result. Once we stratified by household income, only in the below average household income group, store food in hard plastic (MEHHP increase by 37%, p=0.01), scented laundry detergent use & presence (MEHHP decrease by 8%, p=0.03), and mould in bathroom (MEHHP increase by 25%, p=0.04) were significantly associated with MEHHP metabolite concentrations, but this is not the case for the above average household income group anymore.

3.3.6 Tobit regression model – MEOHP phthalate metabolite

For MEOHP phthalate metabolite concentrations, there were 178 subjects' concentrations that were left censored values.

Table 3.3.6 reports the exposure sources that were found to be associated with urinary phthalate metabolite MEOHP concentrations in final regression models. Holding all other potential exposure sources in our final model constant, subjects who have mould in the bath that baby uses have 33.38% (p=0.0002) higher urinary MEOHP concentration than those who do not have mould in the bathroom.

We found use of plastic bowl (MEOHP increases by 17.73%, p=0.0056), bathroom tile cleaner (MEOHP increases by 6.59%, p= 0.0182), air fresheners (MEOHP increases by 6.95% p=0.0219), and vinyl floor in kitchen (MEOHP increases by 38.68%, p=0.0370), were significantly associated with MEOHP phthalate metabolite concentration.

Some of the negative associations we found did not agree to other studies, visible evidence of mould in the living room that baby slept (MEOHP decreases by 20.59%, p=0.013).

Table 3.3.6 MEOHP and potential exposure sources (N=577)

Tobit Model (MEOHP) P=0.10							
Variables	**Type**	**% of Exposed**	**Parameter Estimate**	**Standard Error**	**95% Confidence Limits**		**Pr > ChiSq**
Is there any MOULD in the bathroom, baby use?	Binary	89.80%	33.38%	0.0338	0.0589	0.1914	0.0002
Did you breastfeed baby for any duration (more than a few days) since birth?	Binary	93.20%	-41.66%	0.0682	-0.368	-0.1	0.0006
Is the child sleeping alone in this bedroom?	Binary	60.20%	-22.34%	0.0339	-0.176	-0.043	0.0012
How often do you use a plastic bowl to serve your baby's food?	Ordinal	5.70%	17.73%	0.0256	0.0207	0.1211	0.0056
Are there visible signs of MOULD in Living room, baby slept?	Binary	86.20%	-20.59%	0.0404	-0.179	-0.021	0.0133
Bathroom tile cleaner in use & Presence	Ordinal	68.10%	6.59%	0.0117	0.0047	0.0506	0.0182
Plug-in air freshener in use & Presence	Ordinal	22.20%	6.95%	0.0127	0.0042	0.0542	0.0219
Baby shampoo	Binary	86.20%	-13.64%	0.0285	-0.12	-0.008	0.0254
Tobit Model (MEOHP) P=0.10							

Variables	Type	% of Exposed	Parameter Estimate	Standard Error	95% Confidence Limits		Pr > ChiSq
Hard vinyl (tiles) - Kitchen	Binary	7.00%	38.68%	0.0681	0.0086	0.2755	0.037
Disposable diapers	Binary	93.70%	-24.11%	0.0673	-0.252	0.0122	0.0752
Drain cleaner in use & Presence	Ordinal	38.90%	9.37%	0.0224	-0.005	0.0828	0.0816
Hard vinyl (tiles) - Bathroom, baby use	Binary	86.00%	-15.82%	0.0453	-0.166	0.014	0.0988

Table 3.3.6a MEOHP stratification analysis (Household income above average vs. below average)

	Stratified Analysis Household income > = Average		Stratified Analysis Household income < Average		Overall Analysis	
Variables	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**	**Effect Estimate**	**P-Value**
Is there any MOULD in the bathroom, baby use?	10%	0.38	34%	0.0029	33.38%	0.0002
Did you breastfeed baby for any duration (more than a few days) since birth?	-36%	0.03	-13%	0.5215	-41.66%	0.0006
Is the child sleeping alone in this bedroom?	-15%	0.11	-2%	0.8829	-22.34%	0.0012
How often do you use a plastic bowl to serve your baby's food?	13%	0.09	3%	0.6667	17.73%	0.0056
Are there visible signs of MOULD in Living room, baby slept?	-14%	0.20	-1%	0.9206	-20.59%	0.0133
Bathroom tile cleaner in use & Presence	3%	0.40	10%	0.0159	6.59%	0.0182
Plug-in air freshener in use & Presence	1%	0.74	8%	0.0714	6.95%	0.0219
Baby shampoo	-22%	0.003	1%	0.8833	-13.64%	0.0254
Hard vinyl (tiles) - Kitchen	18%	0.43	34%	0.1554	38.68%	0.037
Disposable diapers	-12%	0.54	-17%	0.3231	-24.11%	0.0752
Drain cleaner in use & Presence	9%	0.16	17%	0.0442	9.37%	0.0816
Hard vinyl (tiles) - Bathroom, baby use	-11%	0.41	-18%	0.165	-15.82%	0.0988

To get some insight on the effect of SES on the MEOHP metabolite concentration, we then fit the final MEOHP model on the data stratified by household income (Table 3.3.6a). There were five variables, child sleeping alone, use plastic bowl, mould in living room, air freshener in use & presence, and hard vinyl tiles in kitchen were significant in the overall analysis, but they are no longer significant in neither household income above average nor in below average group. Drain cleaner in use & presence, which was found associated with several other metabolites, was not significantly associated with MEOHP at the 0.05 level in the overall analysis. However, once we stratified by household income, we found the drain cleaner in use & presence was became positively associated with urinary MEOHP phthalate metabolite concentration (MEOHP increased by 17%, p=0.04) in the below average household income group.

There were also several explanatory variables that were significant in the overall Tobit analysis, once we stratified them by household income; they were only significant in either above or below average group. For the subjects whose household income below the average, visible mould in the bathroom (MEOHP increases by 34%, p=0.003) and bathroom tile cleaner in use & presence (MEOHP increase by 10%, p=0.02) were found significantly associated with urinary MEOHP phthalate metabolite concentrations, they had the same direction and strength of associations as they are in the overall analysis. For the subjects whose household income above the average, breastfeed (MEOHP decreases by 36%, p=0.03) and baby shampoo use (MEOHP decrease by 22%, p=0.003) remain significantly associated with urinary MEOHP phthalate metabolite concentrations as in the overall analysis, but were not associated with MEOHP anymore in the below average household income group.

4. Discussion

4.1 Findings

There is evidence suggesting that there are correlations between food, plastic furnishes, mould, dust, personal care products and human phthalate exposure individually, and following with health outcomes such as asthma, allergies etc., however, very few studies have collected comprehensive exposure information prior to and immediate after birth. The results of this analysis and combine with 1 year and 3 year results, they will provide longitudinal estimate of exposure to phthalates in Canadian children. In our results we found holding everything else within the model constant, the usage of bathroom tile cleaner was found to be significantly associated with MEP (increases by 7.47%, p=0.0486), MBzP (increases by 6.95%, p =0.05), and MEOHP (increases by 6.59%, p=0.0219); with relative similar strength of associations. This finding could be explained by phthalates being used a scent stabilizer and emulsifier in many of these products (CHRP, 2008 & CFIA, 2011)

In our results we also found the usage of soft plastic as a storage device for breast milk, formula, food or other drinks, or using it as a serving device are also significantly associate with five phthalate metabolites examined here, MBzP, MEHP, MEHHP, and MEOHP. Similarly, holding everything else within the model constant, the use of soft plastic for either storing or serving was found to be significantly associated with MBP (increases by 38.00%, P<.0001), MBzP (increases by 23.08%, p =0.032), MEHP (increases by 48.01%, p =0.0008), MEHHP (increases by 48.01%, p =0.0008), and MEOHP (increases by 17.73%, p =0.0056). This result also agreed to recent studies (Cirillo et al., 2011; Rudel et al., 2011)

However, another interesting finding was that subjects who were breast fed had lower urinary phthalate metabolites; MBzP (decreases by 34.07%, p= 0.031), MEHP (decreases by 49.52%, p= 0.0019), MEHHP (decreases by 49.52%, p= 0.0019), and

MEOHP (decreases by 41.66%, p= 0.0006), with similar strength of associations. However since we didn't measure phthalates in breast milk, we cannot conclude from this result that breast milk has protective effects on phthalate exposure in children. This result contradicts to the results from several studies of phthalates in breast milk, which concluded that breast milk may represent additional sources of phthalate exposure (Latini et al., Main et al., 2006, Zhu et al., 2006).

Above two totally opposite findings shows that breast feeding directly provide lower level of phthalate metabolites concentration in urine, whereas storing breast milk in plastic storages will increase the urinary phthalate metabolite concentrations. Since several studies indicated that phthalates concentration in breast milk is close to or around detection limits (Hines et al., 2008; Högberg et al., 2008), which means if mom feed their breast milk directly to their babies, the chances for their babies to be exposed to phthalates are less than feed them with plastic bottles, which are normally coming with the breast pump boxes.

We identified several negative correlations that we are unable to explain. For example, DEHP is the parent compound for MEHP, has is used in many building materials, such as flooring and roofing, as well as medical supplies, and other widely used application. (Inoue, 2005) However in our analysis, we found negative associations between urinary MEHHP phthalate metabolite concentrations and furnished materials. For example, we found urinary MEOHP phthalate metabolite concentrations were lower in subjects' whose bathrooms had hard vinyl tiles compared with those without hard vinyl tiles (Table 3.3.6). This could be a signal DEHP is being phased out in the indoor building and furnishing industry and it's being replaced by other phthalates.

A finding that hasn't been well documented is the impact of sleeping alone on phthalate exposure. We found for babies who sleep alone, their MBzP phthalate metabolite concentration were 33.09% lower than those who do not, MEOHP phthalate metabolite concentrations were 22.34% lower than those who do not sleep alone. This may be an indication that parental product usage may be an important source of children's exposure through dermal contact and possibly inhalation. This exposure route demands further study.

Koo et al. (2002) found subjects household income less than $1,500 per month prior to sampling and with only high school education had higher estimated BBzP and DEHP exposure. We found similar negative correlations in our analysis only for MEHP decrease by 21% ($p=0.0339$) and MEHHP decrease by 21% ($p=0.0339$), both of MEHP and MEHHP are metabolites of DEHP. We did not find this negative association between MBzP and household income, this may be due to our sample has a higher household income, median household income range from $60,000 to $79,999; however, in our bivariate analysis; we did also find significant negative correlation (Pearson Correlation = -0.09, $p=0.04$) between MBP and household income. In order to further identify the role of household income level in relation to urinary phthalate metabolites concentrations, we further stratified each final Tobit model into above average and below average groups. Some variables were significant associated with urinary metabolite concentrations in their overall Tobit results; they were no longer significant in their stratified results. Subjects who were breast fed had lower urinary phthalate metabolites were no longer significantly associated with MBzP (above average group $P= 0.92$, below average group $p=0.91$), MEHP (above average group $p= 0.39$, below average group $p=0.84$), and MEHHP (above average group $p= 0.0752$, below average group $p=0.3531$). Only for the below household income group, breastfeeding is still negatively associated with urinary MEOHP (decreases by 36%, $p= 0.03$) phthalate metabolite concentration. Another interesting result of stratification analysis is that some variables were not significantly ($0.05 < p <0.10$) associated with urinary phthalate metabolites in the overall Tobit results, they became significant in either below average household income group, or above average household income group. For example, drain cleaner in use & presence were not significant ($p=0.08$) associated with urinary MEOHP phthalate metabolite concentration in the overall analysis, but in the stratified analysis, drain cleaner in use & presence were found positively associated with urinary MEOHP phthalate metabolite concentration ($p=0.04$) in the below average household income group. Similarly, plastic toys in mother's bedroom were significant associated with urinary MEP phthalate metabolite concentration in the above average household income group ($p<0.01$) whereas for the overall Tobit result, it wasn't significant associated with MEP phthalate metabolite ($p=0.07$).

With the stratified analysis, several un-expected negative association also disappeared. For example, in the final MBP multiple regression model, muti-surface cleaner in use & presence (p=0.02), and feed baby with hard plastic bottle (p=0.03) were negatively associated with urinary MBP phthalate metabolite concentration, whereas in their stratified results they were no longer significant.

Based on the differences we found with the stratification analysis, given the health concern associated with phthalate exposures, more research in the area of socioeconomic status and phthalate exposure is needed to elucidate the reason for these findings.

4.2 Limitations

There are some limitations of our study. Even though we attempted to include many potential sources of exposure, there are other sources we did not measure. Phthalates have been found in food (Cirillo et al., 2011; Rudel et al., 2011); perfumes, deodorants and cosmetics (Just et al., 2010). We did, however, measure personal baby care products, such as shampoo and lotion. Still, because the ingredients of many of these products are proprietary, it is likely that we failed to measure some important sources of phthalate exposure. The CHILD study is intending to collect this information at the three years visit.

We did not have information on maternal levels of exposure, such as personal care products, and cosmetics use. We intend to collect this information at three year visit. So far there is no study with large sample size presenting data on both children and their mother's phthalate exposures. If mother's exposure information were included, exposure of other unmeasured factors could be clarified at least for fully breast fed babies.

In our cohort, 92% of babies were breast fed at three months of age. We found that breastfeeding was associated with lower MEHP, MEHHP, and MEOHP metabolite concentrations. Several studies compared phthalate contents in breast milk and other biomarkers, phthalates concentration in milk were consistently around detection limit. . As Högberg et al. (2008) indicated in a Swedish study that most phthalate concentrations had lower detection limits in breast milk samples. At this moment, storing breast milk into plastic storage container should be more important contamination routes as our results indicated.

As noted early, accidental ingestion of dust can be other potential sources of phthalate exposure (Wu et al., 2007; Jones-Otazo et al., 2005). As studies have shown, phthalates can be found in household dust samples, both in settled dust samples and air samples (Bornehag et al., 2005 Kavlock et al., 2002). However, we didn't have dust phthalate concentration results at the time of this analysis; this may also hinder the assignment of exposure.

Consistent with the Swedish study, we also found indoor humidity or water leakage in the home was associated with higher urinary phthalate metabolite concentrations, including higher concentration of urinary BBzP. Scientists hypothesized that bacterial is playing an active role in the phthalate degradation (from parent compound to metabolites) process (Chen et al., 2007). The contribution of moisture in the degradation of phthalates from parent compounds to metabolites needs to be better understood.

Pearson correlations were conducted between different metabolites (Appendix table 3), significant correlations were found between several phthalate metabolites, and however this is reasonable, since we don't know the ingredients for most of the household and personal care products, e.g. There could be DEHP and DEP in bathroom tile cleaner, as DEHP can be used as emulsifier and DEP can be used as scent stabilizer. If one person has higher DEHP from using bathroom tile cleaner, then their DEP should be higher as well, and in this example, we haven't event take into consideration of packaging, as most of these products are in plastic bottles. For our analysis, we modeled metabolites individually instead of using total phthalate concentration as the dependent variable.

Modeling exposure determinants across multiple exposure sources are somewhat less common, possibly due to a lack of available human data or difficulty in compiling data. The methods of our project minimized the issue of traditional multiple regression modeling by including subjects with non-detectable phthalate metabolite concentrations, yet including more exposure sources than traditional studies has additional limitations, including limited information for accurate assessment of determinants, for example, the lack of personal care product ingredients information in this case.

Since we didn't introduce interaction terms into our models, future studies should explore the interaction between all potential independent variables, including potential genetic and epi-genetic interactions. One valid criticism of our approach is that phthalate metabolites with relatively short half-lives (3-12 hours) do not predict long term exposure. However, Hauser et al. (2004) conducted a sensitivity analysis and concluded that a spot urine sample can moderately predict phthalate exposure over the course of three months. To further improve explore this issue, multiple time period sampling should be collected.

4.3 Policy implications

Based on the above results, household care products, personal care products and also plastic storage containers are some of the potential exposure sources for Canadian children at three months of age. However as a consumer, I cannot identify them on any product labels, which means in order to promote public awareness and public health, improvement in policy and regulations are greatly needed.

The regulation on phthalates can be different depending on where you live. The European Union (EU) has taken the precautionary approach on child-care articles, which means manufacturers and suppliers must provide evidence that chemicals such as phthalate will not cause irreparable harm to human health before adding it to products (GC, 2009). In 1999, EU identified phthalates as a priority for action, emphasizing the importance of the precautionary principle to help prevent toxic exposure. (Kopelman et al., 2004) In 2005, the EU banned the use of DEHP, DBP and BBP in the manufacture of toys and childcare articles, which are intended to facilitate child sleep, relaxation, and hygiene, feeding or sucking; combined phthalates cannot exceed 0.1% by weight. Another group of phthalates (DINP, DIDP, and DNOP) that can potentially cause ill health were banned in the products that can be placed in a child's mouth. (GC, 2009)

Table 4.1. Comparison of current policies

	European Commission	California	Canada
DEHP, DBP, BBP	Prohibit: concentration of three phthalates combined CANNOT exceed 0.1% in toys and child care articles - 2005	Prohibit: concentration of three phthalates combined CANNOT exceed 0.1% in toys and child care articles – 2009	Prohibit: concentration of three phthalates combined CANNOT exceed 0.1% in toys and child care articles - 2011
DINP, DIDP, DNOP	Prohibit: concentration of three phthalates combined CANNOT exceed 0.1% in toys and child care articles if it can be placed in mouth by children - 2005	Prohibit: concentration of three phthalates combined CANNOT exceed 0.1% in toys and child care articles if it can be placed in mouth by children - 2009	Prohibit: concentration of three phthalates combined CANNOT exceed 0.1% in toys and child care articles if it can be placed in mouth by children - 2011
Cosmetics	Banned phthalates in cosmetics sold in Europe	None	None

Relatively speaking, in North America, governments have not been proactive in the area of phthalate regulations, as similar bans were implemented four to six years later in California (2009) and Canada (2011). Even though the same policy has been applied in three different regions, the definition of toys and child care articles are different as displayed in the table below:

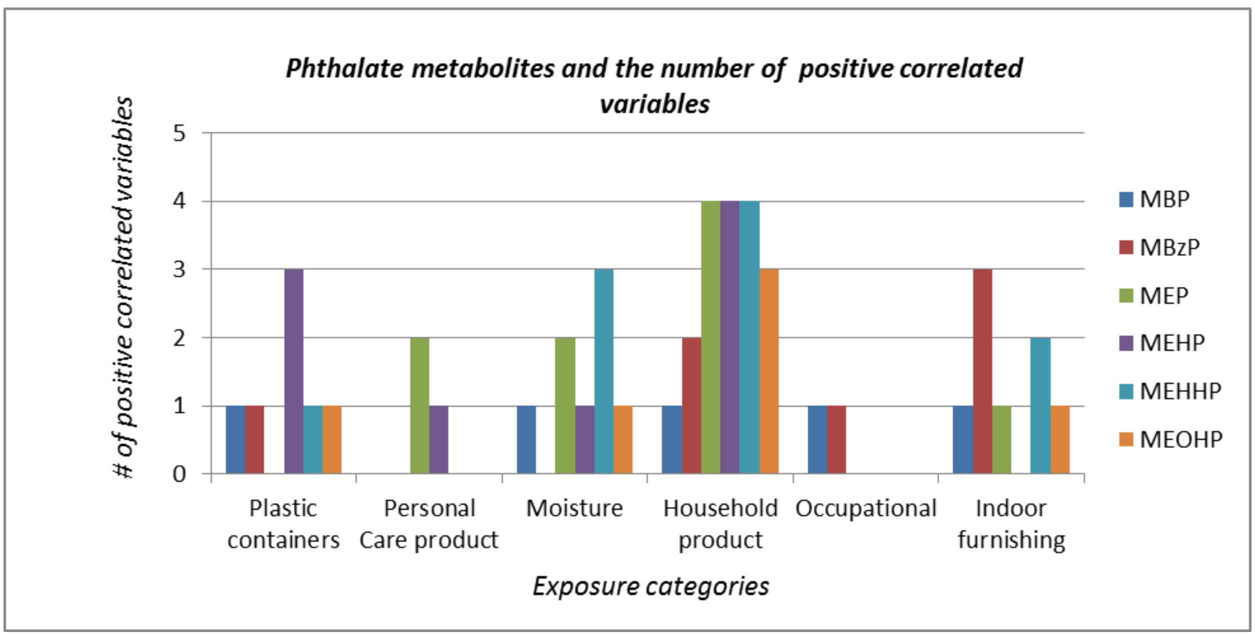
Table 4.2. Comparison of current definitions

	European Commission	California	Canada
Definition of toy	Any product or material designed or clearly intended for use in play by children of less than 14 years of age	All product designed or intended by the manufacture to be used by children when they play, no age specified	Product that is intended for use by a child under 14 years of age in learning or play
Definition of child care articles	Any products intended to facilitate sleep, relaxation, hygiene, the feeding of children or sucking on the parts, no age specified	All product designed or intended by the manufacture to facilitate sleep, relaxation or the feeding of children, or to help children with sucking or teething, no age specified	Product that is intended to facilitate the relaxation, sleep, hygiene, feeding, sucking or teething of a child under four years of age

Information retrieved from HAZARDOUS PRODUCTS ACT, Government of Canada, Vol. 144, No. 26

As multiple epidemiologic studies and results of this project have shown, humans can be exposed to phthalates through a variety of pathways. Toys and child care articles shouldn't be the only concerns as we can also be exposed to these compounds through personal care products, such as baby powders, diaper cream, lotion and shampoos, etc. and household products such as air fresheners and bathroom tile cleaners. Since phthalates are so ubiquitous, removal of phthalates from a variety of industries should be applied. To remove phthalates from all products at once is not reasonable; we should start from the products that correlate with most of the known phthalates, which also contribute the most risk in terms of human development, pregnant moms and children. Based on our analysis as indicated in Figure 4.1, household products have the most number of positive correlated variables with all six interested phthalate metabolites, may be plastic containers and indoor furnishing to follow. Clearly based on t his analysis, we can see by only regulate toys and child care articles is not sufficient, as they are being exposed through other medias such as household products, or the food storage containers etc.

Figure 4.1 Phthalate metabolites and the number of positive correlated variables



Cost benefit relations shouldn't deter us from implementing these regulations. As stated in the cost-benefit analysis for Health Canada, restricting DEHP and possibly additional phthalates, for any particular business in Canada, would have a minimal impact on revenue. Estimates of cost in revenue are less than 1% to a maximum of 5%. The increased cost to the consumer would not be very substantial. [GC, 2009]

We cannot diminish the properties of phthalates which has been used as scent stabilizer, emulsifier, and make plastic flexible; however while we are working on the replacement of phthalate, precautionary principle should be take into consideration, which means all chemical that will be used to replace phthalate should be proved non-toxic to human before being implemented.

5. Conclusion

There is growing evidence that exposure to phthalates is related to a wide range of adverse health effects including asthma, allergies, neurodevelopment, and sperm quality (Lee et al,, 11989; Jaakkola et al., 2000; Kolarik et al., 2008; Moisan et al., 1991; and Huang et al., 2011). We found detectable levels of metabolites MEP, MBP, MBzP, MEHP, MEHHP, and MEOHP in more than 70% of the samples (Table 3.2) suggesting widespread exposure in this cohort to DEP, DBP, and DEHP.

Our analysis demonstrated higher levels of phthalate metabolites associated with household product use, such as bathroom tile cleaner, air fresheners, and personal baby care products such as baby wipes. Associations between the uses of plastics were also correlated with the levels of urinary phthalate metabolites concentrations. The identification of these exposures as contributors to phthalates body burden on three months old children is an important step in exposure categorization and provides evidence for policy making to reduce exposure.

Incorporating Tobit regression modeling method allowed us to include subjects whose phthalate metabolite concentrations were below the detection limits, which increased the total usable number of subjects, and also avoided introducing potential bias to the analysis by using phthalate metabolite concentration imputation methods. This modeling method can predict several phthalate metabolites of interest.

We await the larger CHILD cohort results to enable better understanding of the relationships with other sources of phthalate exposure including food, medication and health outcomes such as allergy and asthma diagnosis.

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Appendices

Appendix A.

Table 1： Bivariate analysis results (P<0.05)

		MBP			
Question	**Type**	**t - Value**	**Pr>|t|**	**Sample Correlation**	**P-Value**
Is there any Leaks in the kitchen?	Binary	-2.10	0.04		
Does baby currently spend any time in this bathroom?	Binary	-3.29	0.00		
Is there any evidence of LEAKS in the bathroom?	Binary	-2.49	0.01		
solvent	Binary	-2.55	0.01		
Use pacifier?	Binary	2.28	0.02		
Are you using disposable diapers on baby?	Binary	2.38	0.02		
Are there members of the household who work with hazardous materials on the job?	Binary	-3.05	0.00		
do you STORE breast milk, formula, food or other drinks in Hard plastic?	Binary	-3.12	0.00		
do you HEAT expressed breast milk, formula, food or other drinks in Hard plastic?	Binary	-2.93	0.00		
How often do you use a plastic bowl to serve your baby's food?	Ordinal			0.10	0.02
Household income	Ordinal			-0.09	0.04
		MBzP			
Question	**Type**	**t - Value**	**Pr>|t|**	**Sample Correlation**	**P-Value**
Earthy, mouldy, musty	Binary	-2.14	0.03		
Is the child sleeping alone in this bedroom?	Binary	2.57	0.01		
Plastic blinds	Binary	2.14	0.03		
Hard vinyl (tiles)	Binary	-2.44	0.02		
dishwasher detergent	Binary	3.38	0.00		
Glass cleaner	Binary	2.20	0.03		
Plastic/foam floor playmats:	Ordinal			-0.10	0.04
Have you brought any major pieces of NEW furniture into your home since you completed the Home Environment Questionnaire during your pregnancy?	Binary	3.51	0.00		
Are you aware of any water leaks/incidents in your home during this period of time?	Binary	-2.40	0.02		
How many people currently live in your home?	Ordinal			0.11	0.03
dishwasher detergent	Ordinal			-0.11	0.03
		MEP			
Question	**Type**	**t - Value**	**Pr>|t|**	**Sample Correlation**	**P-Value**
Basement floor age	Binary	-1.99	0.05		
Is there a child’s bedroom or a bedroom that will become the child’s bedroom?	Binary	2.47	0.01		
Laminate	Binary	2.04	0.04		
Age of floor - Child’s bedroom+A56	Binary	-2.09	0.04		

		MEP			
Question	**Type**	**t - Value**	**Pr>|t|**	**Sample Correlation**	**P-Value**
Paint > 6 months	Binary	2.24	0.03		
Does this room have windows?	Binary	2.64	0.01		
Is there any evidence of LEAKS in the bathroom?	Binary	-2.52	0.01		
dishwasher detergent	Binary	2.00	0.05		
bleach	Binary	-2.03	0.04		
Plastic toys	Ordinal			-0.10	0.02
Baby powder, talc or cornstarch:	Ordinal			0.16	0.00
Other skin products	Ordinal			0.10	0.02
Spray air freshener	Ordinal			0.12	0.01
dusting polish or spray	Ordinal			0.10	0.02
unscented candle	Ordinal			0.09	0.03
scented candle	Ordinal			0.12	0.01
incense	Ordinal			0.13	0.00
Unscented laundry detergent:	Ordinal			-0.09	0.04
Bathroom tile cleaner	Ordinal			0.14	0.00
how often did you feed baby with the Nursing with nipple shields?	Ordinal			0.10	0.04
how often did you feed baby with the Other type of container?	Ordinal			0.12	0.02
		MEHP			
Question	**Type**	**t - Value**	**Pr>|t|**	**Sample Correlation**	**P-Value**
Is the child sleeping alone in this bedroom?	Binary	-2.83	0.00		
Laminate	Binary	2.04	0.04		
Glass cleaner	Binary	-2.38	0.02		
toilet bowl cleaner	Binary	3.05	0.00		
solvent	Binary	-2.78	0.01		
Plastic toys	Ordinal			0.11	0.06
Are you using cloth diapers on baby?	Binary	-2.42	0.02		
Are you using disposable diapers on baby?	Binary	2.02	0.04		
Baby shampoo	Ordinal			-0.12	0.04
Baby lotion	Ordinal			-0.13	0.03
Other skin products	Ordinal			0.15	0.01
eco & organic cleaning product	Ordinal			0.12	0.04
Unscented laundry detergent:	Ordinal			0.15	0.01
Scented laundry detergent:	Ordinal			-0.18	0.00
Fabric softener:	Ordinal			-0.12	0.03
When breastfeeding since birth, did you use a breast pump to express the milk?	Binary	-2.47	0.01		
do you STORE breast milk, formula, food or other drinks in Hard plastic?	Binary	-2.68	0.01		
how often did you feed baby with the Bottle with soft plastic bottle liner?	Ordinal			-0.18	0.00
Are there visible signs of MOULD in the basement?	Binary	-2.51	0.01		
Is there any evidence of LEAKS in the basement?	Binary	-2.19	0.03		
Plastic blinds	Binary	-2.21	0.03		

		MEHHP			
Question	**Type**	**t - Value**	**Pr>|t|**	**Sample Correlation**	**P-Value**
Is there a child's bedroom or a bedroom that will become the child's bedroom?	Binary	2.02	0.04		
Is the child sleeping alone in this bedroom?	Binary	2.36	0.02		
Paint > 6 months	Binary	2.33	0.02		
Does this room have windows?	Binary	1.98	0.05		
Is there any MOULD in the bathroom?	Binary	-3.10	0.00		
Is there any evidence of LEAKS in the bathroom?	Binary	-2.51	0.01		
Does the home have both a family room and a living room?	Binary	2.44	0.02		
Plug-in air freshener (passive) in use	Binary	-2.01	0.05		
dishwasher detergent	Binary	2.04	0.04		
Stuffed toys	Ordinal			0.11	0.02
Have you brought any major pieces of NEW furniture into your home since you completed the Home Environment Questionnaire during your pregnancy?	Binary	2.62	0.01		
Have you used a PORTABLE humidifier/vaporizer in your home since you completed the Home Environment Questionnaire during pregnancy	Binary	2.15	0.03		
How many square feet is your home?	Ordinal			-0.13	0.01
dishwasher detergent	Ordinal			-0.14	0.00
How often do you use a plastic bowl to serve your baby's food?	Ordinal			0.14	0.00
How often do you feed your baby's with plastic utensil?	Ordinal			0.14	0.00
		MEOHP			
Question	**Type**	**t - Value**	**Pr>|t|**	**Sample Correlation**	**P-Value**
Are there visible signs of MOULD in the basement?	Binary	-2.01	0.04		
Plastic blinds	Binary	-2.46	0.01		
Is there any MOULD in the bathroom?	Binary	-2.76	0.01		
Have you brought any major pieces of NEW furniture into your home since you completed the Home Environment Questionnaire during your pregnancy?	Binary	2.39	0.00		
Does the window or mirror in the bathroom where baby spends the most time stay fogged up for more than 15 minutes after a shower or bath?	Binary	-2.50	0.01		
How often do you use a plastic bowl to serve your baby's food?	Ordinal			0.11	0.03

Table 2. Questionnaires and potential independent variables

Questionnaires covered areas	Included in the analysis	Questions related areas	Questionnaire	Potential Exposure Included
Housing structure				
Housing condition				
Housing maintenance history				
Housing renovations				
Indoor housing materials	☺	Floors, walls, blinds & Furniture	b	• Laminate, soft vinyl or hard vinyl floors • Age of wall paint • PVC window covering • Pressed wood, plastic or vinyl floor
Source and extent of dampness indicators	☺	Indoor Moisture	b	• Earthy, moldy or musty odor detected by trained field technicians • Presence/use of humidifier • Condensation on windows in cold weather • Evidence of water leaks during home inspection • Mould seen or suspected during home inspection
Mould growth				
New furnishings				
Appliance emissions				
Presence and type of air conditioning				
Air condition, appliances conditions of use				
Child's and families' time spent in transit				
Mode of transport				

Questionnaires covered areas	Included in the analysis	Questions related areas	Questionnaire	Potential Exposure Included
Frequency/duration of visits to indoor pools				
Exposure to wood smoke				
House cleanliness and cleanability	☺	Cleaning and Chemical Products	a, b	Use (frequency) and presence of household cleaning products: air fresheners, floor cleaner, furniture polish, floor polish, dusting polish or spray, drain cleaner, dishwasher detergent, bleach, multi-surface cleaner, unscented/scented candles, incense, eco & organic cleaning product, glass cleaner, chemical hand cleaner, unscented/scented laundry detergent, toilet bowl cleaner, oven cleaner, bathroom, tile cleaner, solvent (e.g. Nail polish/paint remover)
Type of heating/cooling				
Microbial and chemical contaminant burdens				
Basement condition				
Crawl space condition				
Geographical coordinates				
Baby care product usage	☺	Personal & Child Care Products	a	• Diaper creams • Baby wipes • Baby shampoo • Baby lotion • Baby powder • Pacifier and soft plastic toys/teething rings
Plastic usage	☺	Household plastic ware	d	• Soft/hard plastic container - store, heat food • Soft/hard plastic bottle - store, heat food • Plastic utensils

Questionnaires covered areas	Included in the analysis	Questions related areas	Questionnaire	Potential Exposure Included
Occupational exposure	☺		a	
Pets				
Medication	☺		c	• Capsules
Household income	☺		e	