TOXIC EXPOSURES FROM PERSONAL CARE PRODUCTS

IN WOMEN OF CHILDBEARING AGE

by

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A professional paper submitted in partial fulfillment
of the requirements for the degree

of

Master

of

Nursing

MONTANA STATE UNIVERSITY
Bozeman, Montana

March, 2013
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Amy Elizabeth Lieser
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ACKNOWLEDGEMENTS

Thank you to my family for your continual patience, love and encouragement. This is among many accomplishments made possible only with your abundant support. I would like to acknowledge my committee chair, Dr. Wade Hill, for his expert guidance and encouragement. His passion and dedication to environmental health are an inspiration.
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APPENDIX A: Chemicals found in Personal Care Products and
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A review of current literature suggests an association between the use of personal care products and adverse health outcomes. Significant levels of phthalates, parabens and lead have been detected in many cosmetics. Almost all humans tested have some level of phthalate, paraben and lead body burden. These three chemicals represent a few of the many chemicals prevalent in cosmetics. Human and animal studies link these chemicals with several negative health consequences including endocrine disrupting effects. A review of epidemiology reveals an increasing trend in the prevalence of associated health consequences. In the United States, the cosmetic industry is independently responsible for the safety of cosmetic products. The Federal government has regulatory oversight through the FDA, but does not have authority to test product safety. The Toxic Substance Control Act from 1976 and the Food, Drug and the Cosmetics Act of 1938 represent the most current legislation addressing regulatory standards for personal care products. Nurses advocate for legislation that protects public safety and intervene where public exposures to environmental health hazards are identified.
INTRODUCTION

Background

Human exposure to chemicals has increased over the past 70 years. Both natural and synthetic chemical use has become more prevalent globally and in the United States. Since World War II, chemical production in the U.S. has increased more than twenty-fold and over the past 45 years we have continued to see a steady increase (Federal Reserve Board, 2013). The U.S. Environmental Protection Agency estimated that there were over 84,000 chemical substances in commerce in 2013 (EPA, 2013). Over one million pounds of approximately 3000 of these substances were imported or manufactured in 2012 (EPA, 2012). Contamination of water, air, food, household items, and personal care products is an environmental health hazard.

Industrial chemicals, including lead, phthalates, and parabens, are basic ingredients or contaminants found in personal care products. Research links exposure to these chemicals with multiple, serious, adverse health effects such as breast cancer, endometriosis, endometrial cancer, impaired fertility or infertility, low birth weight, preterm birth, obesity, hypothyroidism, hypercholesterolemia, ADHD, hypospadias, and cryptorchidism. The Environmental Working Groups Skin Deep analysis of commonly used personal care products found more than 20% containing chemicals linked to cancer, 80% with ingredients that commonly contain hazardous impurities, and 56% with skin penetration enhancers (Malkan, 2007; EWG, 2013).
The average adult uses nine personal care products daily, with 126 unique chemical ingredients (EWG, 2008). The average female adult uses 12 beauty products daily and adolescent females use an average of 17 products each day. Consumers are exposed to chemicals through skin absorption, inhalation, and ingestion which can cause systemic effects. Biomonitoring, which measures the types and levels of chemicals in our bodies, demonstrates that chemicals are contaminating our bodies and the environment. The National Health and Nutrition Examination annual survey (NHANES), a national U.S. survey, has consistently found measurable amounts of hundreds of chemicals in humans, including phthalates, parabens, and lead.

The U.S. population is exposed to many different chemicals simultaneously. There is a cumulative effect with the daily use of multiple products. The toxins in these products have been shown to remain in our system, causing effects for decades. More research is needed on the effects of cumulative exposure to chemicals. The National Academy of Sciences recommends against the assumption that there is a safe level of exposure to any individual chemical unless proven otherwise. (National Research Council, 2009).

Our biological susceptibility to harm from chemical exposure varies based on age, health status, and socioeconomic stressors. During periods of development, humans are particularly susceptible to the effects of the endocrine-disrupting toxins found in cosmetics. In women of childbearing age, chemical exposure has the potential to cause adverse health effects to both the cosmetic user and to a growing fetus. Biomonitoring
has clearly shown that every child in the U.S. is born with a burden of multiple chemicals in their body.

The cosmetic industry is self-regulated and their guidelines do not require public release of product ingredients. Most manufacturers label products with some of the intended ingredients, but potentially harmful intended and unintended ingredients are not listed on product labels. Phthalates, parabens, and lead represent three widely used and often unlabeled chemicals found in personal care products. There is increasing global awareness of the toxic effects of industrial chemical ingredients and unintended contaminants. In response, Canada and Europe have increased regulations on personal-care-product manufacturing. Several nonprofit organizations have tested a wide range of U.S. products and found significant amounts of chemicals with potential toxic effects.

**Epidemiology**

Phthalates, parabens, and lead in personal care products have been associated with a variety of health effects in both men and women ranging from endometriosis and infertility to hypospadias and cryptorchidism. Appendix tables 1 through 3 contain a comprehensive list of studies that have found health effects associated with each of the three chemicals of concern.

Associations documented in multiple studies, including Cobellis et al. (2003); Diamanti-Kandarakis (2009); Huang, Kuo, Guo, Liao, & Lee (2007); Lamb IV, Chapin, Teague, Davis Lawton, & Reel (1987); Ormond et al. (2009); Reddy, Rozati, & Raman (2006); Schreder (2009); Swan (2008) and Swan (2010) indicate that phthalate exposure at levels found in cosmetic products may play a role in increasing rates of endometriosis,
endometrial cancer, infertility, hypothyroidism and penile abnormalities in infants. In 1995, Sangi-Haghpeykar and Poindexter reported a 1% to 7% prevalence of endometriosis in women undergoing gynecologic surgery. More recent studies reveal increasing rates of endometriosis. In 2004, 10% to 15% of reproductive-age women had endometriosis (Leibson et al., 2004; Vigano, Parazzini, Somigliana, & Vercellini, 2004). Endometriosis increases the risk of endometrial cancer, which is the most common invasive gynecologic cancer in the developed world. The incidence in Western countries is 10 times higher than in the developing world (Jemal, Siegel, Xu, & Ward 2010). Incidence rates of endometrial cancer increased by an average of 1.1% annually from 2004 to 2008 (Howlander et al., 2008). In 2010, endometrial cancer was the fourth leading cause of malignancy in US women (Jemal et al., 2010). About 30% to 40% of women with endometriosis are infertile, making it one of the leading contributors to female infertility (National Institute of Child Health and Human Development, 2004). In a national survey conducted by the National Center for Health Statistics, the percentage of US women who reported difficulty in conceiving and maintaining pregnancy doubled from 4.3% to 8.3% between 1982 and 2002 (Chandra, Martinez, Mosher, Abma, & Jones, 2005). The increase was most prevalent in women during their peak of fertility, under the age of 25. By 2002, the percentage of infertility or impaired fertility in women ages 18 to 25 was over 12%, an increase of 40% from 1982. According to the CDC (2012b), 11.8% of women between 15 and 44 years old have impaired fertility. In couples that are unable to conceive, 42.2% are due to female etiology and 18.8% are due to male etiology (CDC, 2009a).
Research shows that when pregnant women use cosmetic products containing phthalates, or parabens, the toxins cross the placenta and increase the risk of malformations in the growing fetus (see Appendix A). Between 1988 and 2000 there was a 1.7% increase in congenital penile anomalies (Nelson et al., 2005). Hypospadias is a congenital abnormality where the urethral meatus is located ventral to the tip of the glans in males. Data from the Metropolitan Atlanta Congenital Defects Program and the Birth Defects Monitoring Program (BDMP) revealed that the rate of hypospadias approximately doubled from the 1970s to the 1980s (Paulozzi, Erickson, & Jackson, 1997). The rate of severe cases increased and the ratio of mild to severe cases decreased. The BDMP showed that the increase in hypospadias rates was significant in all four regions of the United States. According to the National Birth Defects Prevention Network (2005), the prevalence of hypospadias or epispadias in the US ranged between 2.01 and 56.17 per 10,000 live births. Cryptorchidism, undescended or maldescended testis, is the most common genital problem encountered in pediatrics. Toparri, Kaleva, and Virtanen (2001) reported that two comparable English studies showed double the incidence of cryptorchidism in full-term boys between the 1950s and the 1980s. According to Medscape (2013), the prevalence of cryptorchidism in the US ranges from 3.7% at birth to 1.1% from age 1 year to adulthood. This incidence of cryptorchidism decreases 1% to 2% after the first few months of life, because congenital cryptorchidism occasionally spontaneously resolves in the presence of the neonatal peak of testosterone by 3 months (Brucker-Davis, Pointis, Chevallier, & Fenichel, 2003). Parabens have been shown to inhibit testosterone by up to 40% (Chen et al., 2007). Cryptorchidism is a risk factor for
testicular cancer. Recent prevalence trend data for cryptorchidism and hypospadias in the US is limited.

A variety of studies have shown that breast cancer, low birth weight, and obesity may be related to paraben exposure (Darbre & Harvey, 2008; Ge & Chang, 2006; Hu et al., 2013; Ishiwatari et al., 2007). Breast cancer is the most prevalent cancer in American women (Moulder & Hortobagyi, 2008). According to Jemal, et al. (2007), twenty six percent of all new cancer cases among women are breast cancer and the average lifetime risk is 12.7%. Breast cancer is the second leading cause of cancer death in women (Moulder & Hortobagyi, 2008). The incidence of low birth weight and premature birth has increased over the past several decades. Donahue, Kleinman, Gillman, and Oken (2010) analyzed almost 37 million non-multiple births from a national database and found that birth weights decreased by an average of 52 grams (1.83 ounces) between 1990 and 2005. Significantly, the study also showed a 1% increase in the number of the lowest-weight babies. In 2010, 8.2% of all U.S. infants were low birth weight (Hamilton, Martin, & Ventura 2010). Low birth weight is associated with neonatal and post neonatal mortality (Mathews & MacDorman, 2008). Low birth weight survivors are at increased risk for several health problems including neurodevelopmental and lower respiratory tract conditions (Goldenberg & Culhane, 2007). The rate of premature births is also increasing. Between 1991 and 2006, premature births increased approximately 30% (Davidoff et al., 2006). Donahue et al., (2010) reported that babies were born an average of 2.5 days earlier in 2005 than in 1990. In 2010, the CDC estimated that 10.7% of infants were born prematurely. In 2012, approximately 12.5% of all births were
premature and this incidence continues to increase. Premature birth is associated with an increased risk of newborn health complications, such as death, learning and behavior problems, and developmental delays (Butta, Cleves, Casey, Cradock, & Anand 2002).

Metabolic syndrome is a combination of disorders including insulin resistance, impaired glucose tolerance, abdominal obesity, reduced HDL-cholesterol levels, elevated triglycerides, and hypertension. All of the disorders that contribute to metabolic syndrome have been increasing over the past 30 years. Obesity has become an epidemic in the United States. In 2012, approximately two-thirds of Americans were at least in the overweight category and about one third were in the obese category. About 5% were morbidly obese. In the US, type 2 diabetes accounts for over 90% of all diabetes cases. Women have a lifetime risk of 35% for diabetes type two and men have a 30% risk (Narayan, Boyle, Thompson, Sorensen, & Williamson, 2003). Studies show that endocrine disruptors, such as parabens and phthalates, may be contributing to this trend. In 2005, the age-adjusted prevalence of metabolic syndrome defined by the International Diabetes Foundation was 43.4% (Athyros, Ganotakis, Elisaf, & Mikhailidis, 2005).

Endocrine disruptors affect nuclear receptor signaling and disrupt hormonal balance, predisposing the individual to all the components of metabolic syndrome (Casals-Casa & Devergne, 2011). Hormones affected, such as estrogen and testosterone, affect body fat distribution and insulin sensitivity. Recent research shows a significant age-independent decline in bioavailable testosterone in American men (Travison, Araujo, O’Donnell, Kupelian, and McKinlay, 2007). This hypoandrogenism is a potential contributor to the increasing incidence of metabolic syndrome.
Lead has been scientifically accepted as a potent neurotoxin for decades. Recent research reveals associations between decreased IQ, decreased mental and psychomotor development index scores, and increased ADHD at lead levels significantly lower than those found in lip gloss and lipstick. Lead may be contributing to the rise in ADHD.

According to the CDC, there was a 22% increase in children with a parent-reported ADHD diagnosis between 2003 and 2007 (CDC, 2011a). The percentage of diagnosed ADHD increased an average of 3% per year from 1997 to 2006 and an average of 5.5% per year from 2003 to 2007 (CDC, 2011a). According to the national comorbidity survey, the prevalence of adult ADHD in 2005 was estimated at 4.4% (Kessler et al., 2006). The extensive list of detrimental health outcomes linked to lead exposure has been well established by the scientific community and accepted by the public. Current research suggests that many of these outcomes may be found at levels found in cosmetic products (Braun, Froehlich, Kahn, Auinger, & Lanphear, 2006; Canfield, 2003; Fewtrell, Kaufmann & Pruss-Ustun, 2003; IPCS, 1995; Lanphear, 2005; Tellez-Rojo, 2006).

Adverse health outcomes associated with cosmetic chemicals are a burden to the individual, family and society. They have financial consequences through lost work and medical bills. The emotional and physical struggle of disease suffering causes decreased quality of life. There is a social impact secondary to employee sick calls and mental disorders. For example, increase incidence of ADHD and other behavior disorders have been associated with increased criminality.

The purpose of this project is to review adverse health effects associated with common chemical ingredients in personal care products, identify contamination of
women of childbearing age from cosmetic chemicals and review the current state of chemical policy as it relates to chemicals in consumer products in the US.
METHODS

Selection of the three chemicals of interest in this review was done in consultation with scientific advisors and conclusions were made based on the prevalence of these chemicals in personal care products. Relevant research concerning the nature of the chemicals reviewed and potential adverse health effects was identified by searching the biomedical sciences databases for primary and secondary research material. Publications from 1990 through the present were preferred but no publication was necessarily omitted due to age. Key articles were retrieved by published journals as indexed on Medline, PsychINFO, ERIC, and The Cochrane Library. In order to ensure the relevant material was not omitted search terms remained broad. Finally, a comprehensive search was conducted for internet resources that included U.S. government databases and nonprofit organizations to identify relevant information not indexed in the professional literature.
Phthalates

Phthalates are composed of a phenyl ring with two attached and extended acetate groups, specifically dialkyl or alkyl aryl esters of 1, 2-benzenedicarboxylic acid. This group of chemicals, typically used as plasticizers, is an aromatic and colorless liquid. Phthalates are used in toys, food packaging, industrial lubricants, solvents, adhesives, flooring, carpeting, shower curtains, laundry detergent, and personal care products. They were originally developed in the 1920s as a plasticizer for food containers, plastic tools, automotive parts, toothbrushes, medical tubing soft plastic toys and other child care articles such as baby bottles (Sathyanarayana et al., 2008). They have non-polymer uses such as dye application agents, adhesives and sealants. In personal care products phthalates are generally used as a solvent for fragrance in perfumes, shampoo, conditioner, shaving products, eye shadows, insect repellants, nail polish, moisturizers, liquid soaps, soap bars, talc, deodorant, and hair sprays and improve the function of the item. For example, phthalates help nail polish spread, fragrances distribute, and give hair spray a better hold. There are dozens of different phthalates. In 2002, Houlihan, Brody, and Schwan tested commonly used personal care products, such as deodorants, fragrances, hair sprays and body lotions. They found phthalates in over 70% of the 72 tested products. Six of the products contained significant amounts of Dibutyl phthalate (DBP), 3 of the products contained Di(2-ethylhexyl)phthalate (DEHP) and 4 products contained Benzylbutylphthalate (BBzP). DBP and Diethyl phthalate (DEP) were found in over 50
percent of the tested products (Houlihan et al., 2002). In 2008, researchers revaluated 17 of the original 72 products with multiple or unusually high levels of phthalates. Five of these products remained high in DEP with levels exceeding 20,000ppm. One of the products contained over double the amount of DEP found in the 2002 evaluation (Archer, Brody, Malkan, & Sarantis, 2008). Sarantis, Naidenko, Gray, and Houlihan (2010) found DEP in 12 out of 17 commonly used perfumes, colognes and body sprays at concentrations ranging from 0.0098% to 3.2% (Sarantis et al., 2010). The Australian government (2011) NICNAS reported that when DEP is used in cosmetics, it is generally imported as an ingredient or as a fragrance base. NICNAS found concentrations of DEP in personal care products ranged from 0.00004% to 34%. DEP is frequently used in conjunction with DEHP or diisononyl phthalate (DINP) (Australian government, 2011). NICNAS evaluations from 2004 and 2006 revealed that DEP is the primary phthalate used in cosmetics and is found in all cosmetic product types. Dimethyl Phthalate (DMP), DBP and Di-n-Octyl Phthalate (DnOP) are also commonly used for applications similar to DEP. Hubinger and Havery (2006) evaluated 48 cosmetic products on the US market and found that DEP was the most frequently used phthalate at concentrations up to 3.9%. Hubinger (2010) conducted a follow-up survey of 84 cosmetic and personal care products available to US consumers and found DEP levels as high as 36 006 μg/g (3.6%) and DBP at a maximum level of 62 607 μg/g (6.3%). Phthlates have clearly been found in a significant percent of commonly used personal care products and in some cases, levels are rising.
Humans are exposed to phthalates through inhalation, dermal absorption and oral intake. According to NICNAS, bioavailability of DEP is 100% when humans are exposed orally or through inhalation. Bioavailability is about 10% with dermal exposure (Australian Government, 2011). Distribution of DEP is widespread. After entering the body, phthalates are broken down into monoester forms. The monoester form is used to measure levels of exposure. For example, mono-methyl phthalate (MMP) is the breakdown product of DMP. When 186 women were tested for mono-ethyl phthalate (MEP), women reporting perfume use had a 2.3 times higher urinary MEP concentration. Phthalate levels increased 7% for each 25% increase in the use of products containing phthalates (Just et al., 2010). In a 2001 to 2002 survey, the CDC found that the mean Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) level in adults in the United States was 18.10 ppb, but significantly higher levels have been found in study participants (CDC, 2005). One woman had 2210 ppb MEP in her urine (Schreder, 2009). Biomonitoring of phthalates through urine samples provides evidence of human body burden.

Blout (2000) tested 289 participants for 7 phthalates and every person tested positive for at least one of the 7 phthalates. All of the study participants tested positive for DBP. Another study showed that 97% of the 2,500 study participants had metabolites of DEP, DBP and Benzylbutyl Phthalate (BBzP) in their urine and 75% tested positive for metabolites of DEHP (Manori, 2001). The U.S. conducts active surveillance for ongoing evaluation of concentration of urinary phthalates through the National Health and Nutrition Examination Survey (NHANES). Significant levels of several types of
phthalate metabolites have been found. Between 2007 and 2008, the 75th percentile of DEP urinary concentrations averaged 2.48 ug/L. Between 2007 and 2008, the 75% percentile of DMP urinary concentrations averaged 7.91 ug/L (CDC, 2012a)

The CDC found that DBP exposures are significantly higher in women of child-bearing age (Blount, 2000). The Washington Toxics Coalition tested nine women during the second trimester and found at least 4 phthalates in all nine women (Schreder, 2009). Phthalates are able to cross the placenta and expose the fetus to phthalates (Wittassek et al., 2009). Human amniotic fluid samples collected in the second trimester tested positive for three phthalates DEP, DEHP and DBP (Silva, Reidy, et al., 2004). Phthalates have been detected in human breast milk indicating potential infant exposure during breast feeding (Hines, Calafat, Silva, Mendola, & Fenton, 2009). In 2008, Sathyanarayana et al. found DEP, DBP, BBP and DEHP in more than 90% of 163 babies tested. Rapidly dividing cells and complex development make the fetus more susceptible to the effects of toxic chemicals. Uterine development begins in the 9th week, breast development begins in the 10th week and ovarian follicles begin to form during the 18th week. The penis and scrotum form in the fifth week and the testes migrate from the abdomen to the scrotum between weeks 28 and 36. The fetus has a limited ability to detoxify the chemicals when compared to adults. Cytochrome P450 enzymes plays a key role in adult detoxification of chemicals. In the fetus, a subset of these enzymes are responsible for detoxification of toxins and are not completely present and active until as late as 24 weeks (Oesterheld, 1998). Fetal metabolism, fat content, and kidney function also play a role in the limited ability of the fetus to detoxify and excrete chemicals. Men and women are both at risk for
exposure and humans are particularly susceptible to adverse effects of phthalates during fetal development.

**Health Effects**

Phthalates have been correlated with an extensive list of adverse health outcomes. Many of these effects are related to their ability to interfere with the endocrine system. For this reason, phthalates are commonly classified as endocrine disruptors (EDs). Health effects are not limited to the reproductive system. Over the past four years, multiple studies link phthalates not only with birth defects in baby boys and reproductive problems in men, but also abdominal obesity, increased diabetes risk, asthma, dermal irritation and thyroid problems (Bornehag et al., 2004; Duty et al., 2003a, 2003b, 2004, and 2005; Hauser et al., 2006, 2007; Huang, Kuo, Guo, Liao, & Lee, 2007; Stahlhut, Van Vijngaarden, Dye, Cook, & Swan, 2007; Wormuth, Scheringer, Vollenweider, & Hungerbuhler, 2006). DEP exposure is also associated with increased liver and kidney weights. Sprague-Dawley rats with 5% DEP added to their food for 16 weeks had increases in relative liver (31%-33%) and kidney weights (11%-17%) (Brown, Butterworth, Gaunt, Grasso, & Gangolli, 1978). The liver appears to be the primary target organ for DEP. When female Swiss mice were given DEP dissolved in corn oil at 0, 10, 25, and 50 ppm significant dose-dependent increases in serum levels of ACP, ALT and AST were found in all treated groups. Liver glycogen, cholesterol and triglycerides were increased in all treated groups. Additionally, intracellular hepatocytic vacuolations were found in all treated groups (Mapuskar, Pereira, & Rao, 2007). Several animal studies (Lamb, Chapin, Teague, Davis Lawton, & Reel., 1987; Heindel, Gulati, Mounce, Russell,
& Lamb IV, 1989; Davis, Maronpot, & Heindel, 1994; & Gray et al., 2000) suggest that phthalates can cause spontaneous abortions, birth defects, altered menstrual cycle, impaired fertility and other reproductive problems. Phthalates decrease testosterone production before and shortly after birth (Lehmann, Phillips, Sar, Foster, & Gaido, 2004; Mylchreest, Sar, Wallace, & Foster, 2002; Parks et al., 2000). This change in hormone production during a critical time of organ development can cause permanent damage.

Four male birth defects, undescended testicle(s), deformity of the penis, low sperm counts and testicular cancer, are collectively called testicular dysgenesis syndrome (TDS). Diamanti-Kandarakis et al., (2009) found that in animals, TDS conditions can be observed after fetal exposure to phthalates. Human males exposed in utero are at increased risk for declined sperm count and quality, hypospadias, and testicular cancer. There are dozens of different phthalates, but DBP, BBzP, and DEHP in particular have been linked with an increased risk of male reproductive health effects (Houlihan et al., 2002). Phthalate exposure is associated with a 2 to 3-fold elevated risk for hypospadias (Ormond et al., 2009). Swan et al. (2010) studied mothers and their children and found that boys born to mothers with higher levels of phthalates in their urine during pregnancy were more likely to exhibit feminized behaviors than boys whose mothers had lower levels of exposure. Swan et al. (2005) found an association between even low-level prenatal exposure to several phthalates and changes in boys’ development, specifically shortening of the anogenital index (distance between the anus and the scrotum, divided by weight). Marsee, Woodruff, Axelrad, Calafat, & Swan (2007) found associations with reduced anogenital distance at phthalate exposures levels significantly lower than current
U.S. EPA reference doses for these chemicals. “The estimated median and 95th percentile of daily exposures to DBP to be 0.99 and 2.68 mcg/kg/day, respectively; for DEP, 6.64 and 112.3 mcg/kg/day; for BBzP, 0.50 and 2.47 mcg/kg/day; and for DEHP, 1.32 and 9.32 mcg/kg/day. (Marsee et al., 2007).” Phthalate reference doses from the U.S. Environmental Protection Agency (EPA) are 100 mcg/kg/day of DBP, 800 mcg/kg/day of DEP, 200 mcg/kg/day of BBzP, and 20 mcg/kg/day of DEHP. Swan (2008) evaluated male offspring of 106 women and study results supported the suspected association between phthalate exposure and smaller penises, undescended testes and feminization. In females, phthalate exposure increases the risk for early puberty, impaired fertility or infertility, preterm labor, endometriosis and breast cancer. Research by Colon, Caro, Bourdony, and Rosario (2000) showed an association between phthalate exposure and premature puberty in young girls. Women with higher blood levels of DBP, BBP, di-octyl phthalate (DOP) and DEHP are more likely to be diagnosed with endometriosis and increased levels of phthalate concentrations correlated with increased severity of endometriosis (Reddy, Rozati, & Raman, 2006). Cobellis et al. (2003) suggests that exposure to phthalates may be contributing to increasing endometriosis rates. Okubo, Suzuki, Yokoyama, Kano, K., and Kano, I., (2003) found that some phthalates increase breast cancer cell proliferation. Additionally, Kim, Han, and Moon (2004), found that phthalates can reduce the effectiveness of antiestrogen treatments such as tamoxifen. In animal studies, phthalates have been associated with dermal irritation. RIFM (1978) found that after a single dermal application of DEP at all concentrations evaluated, all rat and rabbit subjects had redness at the site of application. Phthalates also affect thyroid
function. Meeker (2007) found that higher levels of DEHP breakdown products were associated with lower levels of the thyroid hormone T3. Higher levels of DBP in pregnant women have also been associated with lower levels of the thyroid hormone T4 (Huang et al., 2007). Hatch et al., (2008) found concerning associations between phthalate metabolites and obesity outcomes. Authors reviewed the association between 6 phthalate metabolites and body mass index (BMI) and waist circumference (WC) in 4,369 National Health and Nutrition Examination Survey (NHANES) participants aged 6 to 80 and found significant associations when looking at age and gender specific quartiles. Specifically, females between 12 and 19 years old had an increase in BMI of almost 2 between the first and fourth quartile of mono-2-ethylhexyl (MEP) and females aged 20 to 59 years old had an increase in BMI of almost 1 between the 3rd and 4th quartile (Hatch et al., 2008). Endocrine disrupting (ED) chemicals, such as phthalates, may alter cell signaling involved in weight and lipid homeostasis. There are several possible underlying associations between EDs and obesity, including thyroid and steroid hormone effects and activation of receptors that play a major role in adipocyte differentiation and energy storage. Tang-Peronard, Andersen, Jensen, and Heitmann, (2011) did not look specifically at phthalates, but their research did support the association between EDs, with properties similar to phthalates, and obesity. Stahlhut et al. (2007) reported that phthalate metabolites mono-benzyl phthalate (MBzP), MEHHP, mono-2-ethyl-5-oxohexyl phthalate (MEOHP), MEP were significantly associated with abdominal obesity and MBP, MBzP, MEP were significantly associated with insulin resistance. Phthalates are also strongly associated with asthma and other reactive airway
symptoms. Bornehag et al. (2004) compared 198 young children with asthma and allergies to 202 healthy control subjects. Authors found that subjects whose bedrooms had higher levels of DEHP were more likely to have been diagnosed with asthma. Endocrine disrupting properties of phthalates have effects on multiple systems in the body.

Studies show that a lower level of exposure to several phthalates causes greater harm than the same dose of one phthalate alone. For example, DBP, DEHP and Dibutyl phthalate (DPP) were shown to have a cumulative effect on decreased levels of testosterone. Hauser et al. (2006) reviewed the relationship between PCBs and phthalates on human sperm motility. Authors found that PCBs’ appear to play a role in inhibiting a key enzyme in phthalate metabolism. This finding supports the theory that cumulative exposure to multiple endocrine disruptors can increase adverse effect.

Health effects of phthalates are gaining national and international attention. The Registration, Evaluation, Authorization & Restriction of Chemical substances (REACH) program regulates European personal care products. Phthalates banned under REACH include BBP, DEHP and DBP. These three phthalates were chosen due to evidence of reproductive toxicity in humans and evidence of liver, kidneys, lungs, and reproductive system damage in animals. Even prior to the initiation of the REACH program, the European Union (EU) banned these three phthalates in toys. In 2009, the US banned phthalate use in toys, but there is no regulation regarding phthalate use in personal care products. Policy review shows significant gaps between US and EU cosmetic regulations.
Parabens

Parabens are chemicals made of alkyl esters of p-hydroxybenzoic acid (Tavares, Martins, Oliveira, Ramlho-Santos, & Peixoto, 2009). They are used as artificial preservatives to protect against microorganism which helps maintain product integrity and increases shelf life. Since the 1920s, parabens have been found in anti-microbial agents, cosmetics, body care products, foods and pharmaceuticals. They are more prominent in personal care products that contain significant amounts of water, such as hair care products, moisturizers, sunscreen, facial and shower cleansers, scrubs, and shaving products. They are also found in makeup, toothpaste and antiperspirants. According to the FDA, parabens are the most widely used preservatives in cosmetic products. Several kinds of parabens, including methylparaben (MP), propylparaben (PP), and butylparaben (BP), are commonly found in cosmetics. EWG (2008) measured 6 types of parabens in cosmetics and found that 5 are common, including MP, ethylparaben (EP), PP, isopropylparaben (IP), and BP. Often, multiple types of parabens are used in combination with other preservatives to increase the range of protection against mold and bacteria.

Humans are exposed to parabens through dermal contact, ingestion and inhalation. In vitro and in vivo studies, using healthy human subjects, show that parabens are able to penetrate intact human skin without breakdown by esterases and are absorbed systemically (Darbre & Harvey, 2008). Therefore, topical application of personal care products is one source of paraben presence in the human body. Paraben body burden has been clearly established by multiple studies. Ye, Bishop, Reidy, Needham, and Calafat
demonstrated the presence of urinary conjugates of parabens in humans and reported that urine paraben conjugates could be used as exposure biomarkers to assess human exposures to parabens. Parabens are found in almost all urine samples from U.S. adults of a variety of ethnic, socioeconomic and geographic backgrounds. The CDC tested urine samples in 100 adults and found parabens in nearly all samples (Ye et al., 2006). Smith et al., (2012) collected 2,721 spot urine samples from men and women between 2005 and 2010. The median concentrations were 112 µg/L of MP, 24.2 µg/L of PP, and 0.70 µg/L of BP. Calafat, Fenton, Hines, Mendola, and Silva (2010) analyzed 2,548 urine samples in persons ≥ 6 years of age in the U.S. general population from the 2005-2006 National Health and Nutrition Examination Survey. Authors detected MP in 99.1% of samples, PP in 92.7% of samples, and BP in 47% of samples. The median concentration of MP was 63.5 ug/L and the median concentration for PP was 8.7 ug/L. Concentrations of MP were significantly higher in adolescent and adult females than adolescent and adult males. Authors suspect that the variation in urinary concentrations of MP and PP by sex, race and ethnicity likely reflect the use of personal care products containing these compounds. EWG (2008) tested urine samples from 20 women using an average of 17 personal care products each day and found an average of 115 ppm creatinine urine of MP. Sandanger et al., (2011) reviewed a questionnaire previously answered by post-menopausal women in the NOWAC study and collected plasma samples from 332 of the women. Authors evaluated the connection between plasma concentrations of native parabens and the use of personal care products. They found a significant association between frequent use of skin lotions and elevated concentrations
of native parabens. Native MP was the most prominent (median 9.4 ng/ml), found in 63% of the samples, EP (median < 3 ng/ml) was found in 22% of the samples and PP (median < 2 ng/ml) was found in 29% of the samples. Biomonitoring of paraben body burden in humans through urine sampling continues to provide valuable information for analysis of chemical exposures.

The U.S. National Health and Nutrition Examination Survey (NHANES) found several types of paraben metabolites in urine. Between 2009 and 2010 in the 75th% percentile the urinary concentration of BP averaged 0.600 ug/L. Between 2009 and 2010 in the 75th% percentile the urinary concentration of EP averaged 6.60 ug/L. Between 2007 and 2008 in the 75th% percentile the urinary concentration of MP averaged 204 ug/L. Between 2009 and 2010 in the 75th% percentile the urinary concentration of $n$-PP averaged 44.3 ug/L. Active surveillance through the U.S. NHANES provides a large sample size for exposure analysis (CDC, 2012a).

**Health Effects**

Parabens are used to kill bacteria in water-based solutions, therefore, they inherently have some level of cell toxicity (Ishiwatar et al., 2006). Darbre and Harvey (2008) reported that in vitro and in vivo studies show that parabens have oestrogen agonist properties, androgen antagonist activity, and genotoxic activity. Several lab studies indicate that parabens are endocrine disrupting compounds (Byford et al., 2002; Darbre et al., 2002, 2003; Gomez et al., 2005; Inui et al., 2003; Oishi, 2001, 2002; Pugazhendhi, Sadler, & Darbre 2007). Parabens mimic estrogen by binding to estrogen receptors on cells and increase the expression of genes usually regulated by estradiol
Estrogenic properties of parabens are a concern for human health risks. Intact paraben esters have been found in breast tumors (Ishiwatar, 2006). Darbre et al. (2004). Estrogen-like properties of parabens may influence breast cancer. Ge and Chang (2006) reported that in animal studies parabens are associated with uterotrophic effects in vivo, damage to late stages of spermatogenesis, reduction in sperm quantity in the epididymis and sperm motility in male offspring, and alterations in body weight of offspring. Specifically, parabens can compete with estradiol for binding to the estrogen receptor and increase the proliferation of two estrogen-dependent cell lines. Additionally, parabens increase the expression of both transfected and endogenous estrogen-regulated genes. Parabens are suspected to further decrease reproductive potential through their interaction with mitochondrial function in the testis (Tavares et al., 2009). By interacting with these fundamental cell interactions, parabens cause multiple adverse health effects.

Animal studies show that parabens promote adipogenesis (Hu et al., 2013). The amount of fat cell growth associated with parabens increases with longer linear alkyl chains in a specific order. These results suggest that parabens may contribute to the obesity epidemic. In a sample of 860 children, Savage, Matsui, Wood, and Keet (2012) found parabens to be significantly associated with allergic sensitization. The risk of aeroallergen sensitization significantly increases with higher levels of PP and BP. Chen et al., (2007) found that $p$-hydroxybenzoic acid and its derivatives have no androgenicity at concentrations between $10^{-3}$ and 10 μM. However, at the highest concentrations tested (10 μM), methyl-, butyl- and propyl-4-hydroxybenzoate, authors found significant inhibition of the transcriptional activity of testosterone by 40%, 33% and 19%,
respectively. Testosterone plays a major role in multiple body functions and its inhibition creates a hormone imbalance.

Frequently, parabens are used in combination. Therefore, it is important to review health risks of compound paraben use in addition to single paraben use. Chang, Ge, and Liang, (2007) studied the estrogenicity of single PP, BP, di-n-butyl phthalate (DBP), and their joint treatment in immature female rats. The lowest observed effect level (LOEL) for estrogenic activity of PP was detected at 400mg/kg and estrogenic activity of BP was detected at 200mg/kg. Uterus proliferation effects were observed with joint PP and BP treatment at the doses of 1 and 1/2 LOEL. DBP used with PP or BP increased uterus proliferation effects. Therefore, joint treatment of a combination of DBP, PP or BP could enhance estrogenic activities.

In 1984, the CIR reviewed the safety of MP, PP, and BP. They concluded that these three parabens are safe in cosmetics at levels up to 25%. According to the FDA, parabens are safe at levels ranging from 0.01 to 0.3%. Recommendations do not account for the use of multiple parabens in a single product or for exposure to parabens from several products by a single individual. The EU REACH program banned several parabens including isopropyl, isobutyl, pentyl, phenyl, and benzyl esters of 4-hydroxybenzoi acid. In Australia the NICNAS prohibits the use of DEP in cosmetic products, fragrances, sunscreens or personal insect repellents in preparations containing over 0.5%. Legal variation between organization recommendations based on available research indicates the need for re-evaluation and updated policy.
Lead

Lead is a heavy metal. Its atomic number is 82, relative atomic mass is 207.19, and specific gravity is 11.34 (IPCS 1995). Lead is an unintended contaminant or impurity that has been found in color additives and in other common ingredients, such as water, used to make cosmetics. In 2007, an independent lab tested 33 brand name lipsticks from Boston, Hartford, San Francisco and Minneapolis. Sixty one percent contained detectable levels of lead, with levels ranging from 0.03 to 0.65 ppm. One third of the lipsticks contained lead levels above 0.1 ppm and none of the lipsticks listed lead as an ingredient (Campaign for Safe Cosmetics, 2011c). In a 2010 investigation, the FDA found lead in 400 lipsticks tested with levels ranging up to 7.19 ppm (FDA, 2012). Maybelline Color Sensation made by L’Oreal USA was found to have levels more than 275 times the level found in the least contaminated brands, and more than seven times higher than the average found in all lipsticks. In the 2011, Environmental Defense Canada evaluated 49 face makeup products and found lead in 20 percent of the products. The highest levels of lead (110ppm) were found lip gloss. Lead content in personal care products has clearly been established.

Humans are exposed to lead through inhalation, dermal absorption and oral intake. The National Health and Nutrition Examination Survey (NHANES) for 2003 to 2004 detected 99.6% lead exposure in adult subjects. NHANES evaluates annual averages of blood lead levels (BLL) in US citizens. Between 2009 and 2010 in the 50% percentile the average BLL was 1.70 ug/dL (CDC, 2012a). Average blood lead levels have declined significantly since 1976 when lead was removed from paint, but body
burden continues from exposure to sources other than paint. ATSDR (2010) discusses absorption and distribution of lead in the body. Up to 70% of ingested lead and almost 100% of inhaled lead is absorbed and rapidly developing children absorb higher percentages than adults. Lead crosses the placenta and therefore oral exposure to lead in pregnant women, such as with lipstick use, translates to a significant fetal dose. Fetal exposure to lead is determined by maternal body burden of lead, which can be mobilized from maternal bone during pregnancy and cross the placenta (Amitai et al., 1999). Once absorbed, lead is first distributed to the blood and then to soft tissues such as the liver, kidney and brain. When a person is chronically exposed to lead, 90% is deposited in the bone where elimination takes decades. Lead is also stored in the teeth. Campaign for Safe Cosmetics (2011b) estimates that elimination of accumulated lead in the body takes over 40 years. Lead can be measured in the blood, teeth or bones. However, bone and tooth measurements reflect cumulative exposure while serum levels reflect more current exposure. Needleman et al. (1979) used teeth as a cumulative biomarker for lead exposure and was the first to show that low levels of lead intoxication could cause neuropsychological deficits, a loss of intellectual capacity and non-adaptive changes in behavior. Wasserman et al. (2003) determined that bone lead measurement is a better predictor than BLL indicating that since much of our research is based on BLL measurements, researchers are likely underestimating levels of lead exposure. However, due to the cost, consistency and ease of BLL, it continues to be the preferred measurement tool. While lead use in petrol, paint, plumbing, and solder has been significantly reduced, cosmetics remain a significant source of exposure.
Health Effects

Lead is one of the most studied heavy metals. It accumulates in the body and is toxic to multiple body systems, including the neurologic, skeletal, reproductive, hematologic, gastrointestinal, immune, endocrine, cardiovascular, and renal systems. In 1904, Gibson published the first article to directly link lead-based pain to disease in childhood, but the association between lead exposure and adverse health effects dates back to 1848 when Tanquerel des Planches reported that children placing lead painted toys in their mouths and developing lead colic. Gibson’s (1904) findings revealed blindness, convulsions, and eventually death in children secondary to lead poisoning. Pruss-Ustun, Fewtrell, Landrigan, and Ayuso-Mateos (2004) describe lead as a toxic metal that has caused extensive global health problems, accounting for approximately 0.6% of the global disease burden and 143,000 deaths in. According to Landrigan, Schechter, Lipton, Fahs, and Schwartz (2002), the burden of disease for lead poisoning is 20 times higher for asthma and 120 times higher than cancer. Lead body burden is a significant cause for concern to human health.

Adverse health effects of BLL above 10ug/dL have been well documented and publically accepted for decades. Recent research suggests that there are toxic effects below 10 ug/dL. Tellez-Rojo et al. (2006) found that blood lead levels of less than 10ug/dL at 24 months were significantly associated with a decrease in Mental Development Index and Psychomotor Development Index scores. Based on a linear model, Canfield et al. (2003) found that with each increase of 10 mcg/dL in lifetime average blood lead concentration there was an associated 4.6-point decrease in IQ.
However, for the subsample of children whose maximal lead concentrations stayed under 10 mcg/dL the change in IQ associated with a given change in lead concentration was greater. According to Fewtrell (2003), small effects on intelligence quotient (IQ) are seen with BLL at least as low as 5 μg/dl, and the effects gradually increase with increasing levels of lead in blood. Lanphear et al. (2005) reported that when measuring BLL under 10 mcg/dL the harm is proportionately greater at the lowest BLLs measured. For example, at 10 to 20mcg/dL BLL IQ dropped 2-2.5 points, but at BLL less than 10 mcg/dL, IQ dropped 6 points. Braun, Froehlich, Kahn, Auinger, and Lanphear (2006) used NHANES 1999-2002 results to reveal that subjects with BLL of 2mcg/dL to be twice as likely to have ADHD and four times as likely with BLL between 2 and 4mcg/dL. The results of these studies suggest that more US children may be adversely affected by environmental lead than historically estimated. WHO is currently reviewing and may revise the blood lead action level. Fetuses, infants, young children and pregnant women are most susceptible to health effects from lead for several reasons. The intake of lead per unit of body weight is higher in humans of smaller size. Women use more personal care products containing lead than men. Specifically, lipstick is directly ingested and lead absorption in the gastrointestinal tract is higher. In the fetus, the blood–brain barrier is not fully developed and therefore neurological effects from lead occur at lower levels. Consideration of health effects to both the pregnant woman and the fetus indicate significant consequences of personal care product use.

Lead disrupts calcium and iron in the body and form complexes that effect enzyme systems and lead to multisystem effects (Grandjean & Landrigan, 2006).
According to Tomas Guilarte from John Hopkins, the hippocampus is the key brain structure for learning and memory. It is also very sensitive to lead. Lead is a potent and selective inhibitor of the NMDA receptor subtype of glutamate receptors. NMDA receptors are highly expressed in the hippocampus, playing a role in brain development, synaptic plasticity and neurodegeneration. Lead exposure has been linked to hyperactivity, restlessness, behavioral disturbances, aggression, ADHD, learning disabilities, neuropathy, anorexia, vomiting, constipation, abdominal pain, basophilic stippling and anemia. Based on NHANES 1999-2002, Braun et al. (2006) estimates that 20% of ADHD diagnoses are due to lead exposure. BLL over 70 are now rare, but health effects such high levels include headache, lethargy, coma, and seizures. WHO estimated that, for each 10 $\mu$g/dL increase in lead exposure, height decreases on average by 1 cm. Selevan et al. (2003) indicates that lead may be associated with delayed puberty in girls. Lead exposure is also associated with peripheral neuropathy, motor weakness, weakness of the extensor muscles of the hand (wrist drop). Cave et al. (2010) found lead exposures associated with unexplained ALT elevation and a dose dependent association between lead and suspected NAFLD. Lead hepatotoxicity is well recognized and was recently reviewed by Mudipalli (2007). Regardless of the route of exposure, a large portion of lead gets distributed into the liver. The liver lesion that develops secondary to lead exposure is called “lead-induced hepatic hyperplasia.” Lead increases liver and serum cholesterol levels, oxidative stress, proinflammatory cytokine production and sensitivity (Aykin-Burns, Laegeler, Kellogg, & Ercal, 2003; Kojima, 2004). Cave et al. (2010)
points out that ALT may be normal in NAFLD and therefore low level lead exposure may present an even greater risk for liver disease than recognized by the their study.

In a prospective cohort study of 249 children from birth to two years of age Bellinger, Leviton, Waternaux, Needleman, and Rabinowitz (1987), showed a correlation between BLL in the umbilical cord and damage to early cognitive development. The findings also revealed the potential for lead to cause damage at levels much lower than levels shown to cause overt symptoms. Children were divided into three groups based on UCB levels (low, 3mcg/dL; medium, 6 to 7 mcg/dL; or high ≥ 10 mcg/dL) and found that the high group scored lower on the Bayley Scales of Infant Development that in the low and medium group. In 1987, when the study was published, the CDC defined the highest acceptable BLL in young children as 25 mcg/dL. Lead exposure in pregnant women increases the risk of miscarriage, stillbirth, premature birth and low birth weight, and fetal malformations (IPCS, 1995). Amitai et al. (1999) found a strong correlation between blood lead levels in mothers and their newborns. Authors showed the average BLL of a newborn to be about 90% of their mother’s level. Such a significant increase in fetal body burden supports the suggested link to fetal health effects.

Scientific evidence of harmful effects related to lead exposure emerged between 1970 and 1990 leading the CDC to lower the blood lead action level from 40mcg/dL to 10 mcg/dL in 1991 (ATSDR, 2010). The CDC reports that there is no safe level of lead in children (Campaign for Safe Cosmetics, 2011b). The FDA recommends 0.1 ppm as the upper limit for lead in candy. In Canada, lead is banned as an intentional cosmetic ingredient, but if lead is present as a product impurity, the company is not required to list
it on the label (Environmental Defense Canada, 2011). Health Canada considers 10ppm of lead as “technically unavoidable” as a metal impurity. After evaluating 20 lipsticks, the FDA determined that 1.07 ppm of lead in lipstick is unavoidable and the lowest level of lead that lipstick manufacturers can feasibly achieve is below .026 parts per million (FDA, 2012). Manufacturers can decrease the amount of raw material contaminants, such as lead, by using plant-based colorants instead of petroleum or tar based colorants. With awareness of clear solutions to lead contamination in cosmetic products, manufacturers have the knowledge necessary to eliminate lead from personal care products.

**Policy**

There are several national and international organizations that play a role in voluntary and legal evaluation of personal care products. Key U.S. non-profit organizations include the Campaign for Safe Cosmetics (CSC) and the Environmental Working Group (EWG). Major cosmetic industry organizations include the International Fragrance Association (IFRA), the Research Institute for Fragrance materials (RIFM), the Personal Care Product Association (PCPA), the Cosmetics Ingredient Review (CIR) and the Cosmetic, Toiletry, and Fragrance Association (CTFA). International cosmetic regulatory parties include the European Commission’s scientific committee on cosmetic products and non-food products (EU SCCNFD), Canadian Department of Justice, the Australian Government Department of Sustainability and the International Cooperation of Cosmetics Regulations (ICCR). The cosmetics industry is self-regulated by the IFRA, RIFM, CIR and PCPA. CSC and EWG have published recent research revealing
unlabeled hazardous chemicals in frequently used personal care products. Significant
gaps exist between information reported by the cosmetic industry and nonprofit
organizations. The European, Australian and Canadian government regulates cosmetic
safety. In the US, the FDA has regulatory oversight but the authority to determine
product safety is the responsibility of the cosmetic industry.

Federal Law

US Federal Law passed the Toxic Substances Control Act (TSCA) in 1976. This
law continues to be the primary law responsible for ensuring that chemicals are safe,
including those found in personal care products. In 2008, U.S. Congress passed and
President Bush signed into law the Consumer Product Safety Improvement Act, which
banned 6 phthalates from children’s toys. Phthalates have not been banned from cosmetic
products in the U.S. Existing law for the regulation of cosmetic ingredient safety is the
Food, Drug and Cosmetics Act of 1938. This Act includes about 100 pages of standards
for food and drugs, but only 3 pages for cosmetics (FDA, 2011) and does not authorize
FDA pre-market approval of cosmetic ingredients. While the FDA requires companies to
test drugs and medical devices for safety before marketing to the public, this does not
apply to beauty products (FDA, 2013b). There is one exception. Color additives, except
for coal tar hair dyes, are subject to pre-market approval in cosmetics if they come into
contact with the body for a significant amount of time (FDA, 2007b). Cosmetic
manufacturers are not required to register their cosmetic facilities, file data on
ingredients, or report cosmetic-related injuries to the FDA. Because the cosmetic industry
is not required to report cosmetic facilities with the FDA, the FDA is not aware of how
many companies make and distribute personal care products. The cosmetic industry is responsible for the safety of cosmetic ingredients, preservatives, and co-formulations (Ross, 2006). The FDA does have regulatory oversight of the cosmetic industry and can legally restrict cosmetic ingredients if they are unsafe (Ross, 2006), but since cosmetic manufacturers and suppliers are not required to register with the FDA, report serious adverse effects or comply with FDA regulations, the FDA relies on voluntary reporting of cosmetic ingredients, injuries, adverse effects and establishments to identify products for recall (FDA, 2009a). In 1990, the FDA reported that 3% of personal care product suppliers were reporting injuries (GAO, 1990). It is against the law to market an adulterated cosmetic in interstate commerce, and the FDA can, through an extensive process, regulate cosmetic products after they are released to the marketplace, but the cosmetic industry must initiate the process. The FDA can request, but not require a recall. According to FDA (2005), cosmetic recalls are a voluntary action initiated by the manufacturer or distributor with the intention to remove the products from the market due to gross deception, hazard or defect. The FDA then reviews the product and determines if there is a violation of the FD&C Act. “The FDA is not authorized to require recalls of cosmetics” (FDA, 2005). For example, the FDA could not issue a mandatory recall of Brazilian Blowout hair straightening products even after they were found to contain formaldehyde (Switalski, Malkan, & Hendricks, 2010). In order to remove a misbranded or adulterated product from the market, the FDA must go to court. The FD&C Act defines adulterated cosmetics as containing poisonous or deleterious substance that may cause injury, containing any filthy, putrid, or decomposed substance, prepared, packed, or
held under insanitary conditions, supplied in a container composed, in whole or in part, of any poisonous or deleterious substance, or containing an unsafe color additive within the meaning of section 721(a) of the FD&C Act (FDA, 2005).

Most of the cosmetic ingredients in use today didn’t even exist in 1938, when the FD&C Act was passed. This law has never been significantly amended. The Safe Cosmetics Act of 2011 (H.R. 2359), introduced on June 24, 2011, would have given the FDA the authority to regulate the safety of personal care products and ensure that ingredients are fully disclosed. This bill, a re-introduction of H.R. 5786 (111th) from the previous session of Congress was never reported and never reached the House. Specific provisions of the Safe Cosmetics Act of 2011 include the phase-out of ingredients linked to cancer, birth defects and developmental harm, creation of a health-based safety standard with protection for vulnerable populations, elimination of labeling loopholes, worker access to information about unsafe chemicals in personal care products, required data-sharing to avoid duplicative testing, encouragement of the development of alternatives to animal testing, and adequate funding for the FDA Office of Cosmetics and Colors for oversight of the cosmetics industry.

State Law

Some states have passed state-level legislation regarding cosmetic safety. In 2005, California passed the Safe Cosmetics Act, which requires manufacturers to report any ingredient on the state or federal list of chemicals that cause cancer or birth defects, such as DEHP and DBP to the state. In 2007, Washington State passed the Children’s Safe Products Act, banning phthalates from children’s products, including children’s personal
care products. As a result, the California Safe Cosmetics Program requests information from companies and reports the data to the public.

Evaluation of Ingredients in the Cosmetic Industry

The Personal Care Product council (PCPC), whose membership covers over 80 percent of personal care products on the market, started and funds the CIR. The CIR was created in 1976 to evaluate ingredients in beauty products. The CIR review process is a voluntary industry program and is the only systematic examination of individual cosmetic safety ingredients. Therefore, the approximately $50 billion dollar cosmetic industry is funded and self-policing by the CIR Panel, which is responsible for the safety of personal care products. In its review, the CIR focuses on the safety of single ingredients at one point in time rather than cumulative effect of exposures over a lifetime, aggregate exposures with other toxic chemical exposures, occupational exposure, or vulnerable developmental time periods related to chemical. As of 2009, the CIR reported that it had reviewed about 1,500 ingredients, which accounts for over 80 percent of the ingredients commonly used in cosmetics. Cosmetic industry officials estimate the total number of ingredients used is about 2,000 (Solomon 2004). The FDA (2007) however, estimates that there are about 12,500 ingredients in personal care products, which means that 1,500 ingredients represent about 12% of ingredients used in cosmetics. As of 2008, EWG had formed a database of 29,037 products with 8,821 unique ingredients. This information is available to the public online through the skin deep cosmetic safety data base. In 2008; the FDA had no record of 4,755 of the ingredients in the EWG database. At the current
pace, the CIR will require over 2.5 centuries to evaluate the safety of all current personal care product ingredients in the cosmetic industry.

**Voluntary Review**

There are voluntary standards that personal care product companies can choose to follow. Since 2007, the IFRA has set voluntary standards for fragrances. Since 1976, the Personal Care Product Association’s (PCPA) CIR has set the standards for other cosmetics ingredients in the US (Sarantis et al., 2010). If there are violations to the IFRA standards, the supplier’s name is listed on the IFRA’s website as not complying with the IFRA Code of Practice. IFRA has banned or restricted about 150 ingredients from fragrances (IFRA, 2010). IFRA’s recommendations are based on the Research Institute for Fragrance Materials (RIFM) research. The IFRA uses the RIFM database for safety and testing information on over 3,100 fragrance ingredients (Sarantis et al., 2010).

The FDA’s has a voluntary cosmetic regulations program, where participating cosmetic makers and distributors report product ingredients to the FDA, which can then notify companies if a certain ingredient is found to be potentially harmful based on available research.

The Campaign for Safe Cosmetics, a nonprofit organization, worked with 322 cosmetics companies to meet goals of the compact for safe cosmetics. The compact of safe cosmetics reflects the campaign’s voluntary pledge to avoid chemicals banned by health agencies outside the U.S. and to fully disclose product ingredients. Over 100 companies are also making progress toward meeting the requirements of the compact (Campaign for Safe Cosmetics, 2011a).
Restricted Chemicals in the U.S.

As of 2000, the FDA had banned or restricted 11 chemicals for use in cosmetics and the CIR listed 9 ingredients as unsafe for use in personal care products (CIR 2006). In 2008, Jane Houlihan of EWG reported that an EWG review of U.S. products found almost 400 with chemicals restricted from cosmetics in other countries. Also, over 400 of the products contained ingredients that the CIR and IFA reported as unsafe when used as directed on product labels.

European Union and Australia

The EU’s regulation and disclosure policies on chemicals linked to adverse health effects in cosmetics and personal care products are more stringent and transparent than the US’s. The European Universal health care system requires all citizens to contribute to the cost of health insurance and ensures that every resident of a region has access to required medical services. Since citizens share the cost of healthcare, there is a shared interest in regulation that promotes disease prevention and decreases individual costs for everyone. The EU recently updated legal regulations for personal care products. The Registration, Evaluation, Authorization & Restriction of Chemical Substances (REACH) program, put into action June 1, 2007, is the European Community Regulation law on chemicals and their safe use. REACH increases protection of human health and the environment through earlier identification of the intrinsic properties of chemical substances through increased industry responsibility. Manufacturers are responsible for managing the risks from chemicals and are required to provide safety information on substances in their products. Manufacturers and importers are required to collect
information about the safety of product ingredients, including safe handling. They are also required to register the information in a central public database run by the European Chemicals Agency (ECHA). As safety information is gathered, the law requires manufacturers to progressively substitute chemicals with safer alternatives. REACH will phase in provisions of the law over 11 years. A driving force in the development of REACH was the recognition by the EU that there was insufficient information on the human and environmental hazards of a large number of substances manufactured and sold on the EU market. The REACH program plans to improve available information to ensure that the industry is able to assess hazards and risks of the substances. The industry can then responsibly identify and implement the risk management measures to protect humans and the environment.

European cosmetic facilities are prohibited from selling personal care products made with chemicals that are known or suspected to cause cancer, genetic mutation, reproductive harm or birth defects. Europeans have 5 annexes to their Cosmetics Regulation, classifying thousands of substances as permitted for certain uses, restricted, or banned in cosmetics. The EU has a history of proactive chemical substance regulation. In 1999, the European Union’s SCCNFP published a list of substances known to cause allergies. This list included 24 chemicals that are commonly found in personal care products. The EU now requires that these allergenic substances be labeled on personal care products when their concentration in a leave-on product exceeds 0.001 percent (10 parts per million) (Sarantis et al., 2010).
The REACH program will continue to increase available information related to the potential and known hazards of substances found in personal care products. In the US, cosmetic manufacturers are legally allowed to produce safer products for distribution in Europe while supplying products with ingredients banned as toxic by the EU to the US.

In Australia, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), in conjunction with the Australian Government Department of Sustainability, Environment, Water, Population and Communities (SEWPaC), assesses the safety of industrial chemicals. The NICNAS was established by the Industrial Chemicals (Notification and Assessment) Act 1989, which came into operation on 17 July 1990. The NINAS has two assessment programs, including assessment of environmental effects of new industrial chemicals prior to importation or manufacture, and assessment of chemicals already in use in Australia. The NINAS has created a list of priority chemicals that are now subject to specified restrictions. Manufacturers and importers of these existing priority chemicals are required to apply for assessment and must report any new information to NICNAS. DEP is among the many existing priority chemicals and must be labeled on cosmetics and toiletries (Australian Government, 2011).

Canada

In Canada, cosmetics are regulated by the Food and Drugs Act. Section 16 of the Act states that the sale of any cosmetic that “has in or on it any substance that may cause injury to the health of the user when the cosmetic is used” is to be prohibited (Health Canada, 2009).
In Canada, the government created a Cosmetic Ingredient Hotlist that lists hundreds of restricted chemicals and cosmetic ingredients (Health Canada, 2011). The hotlist, however, does not apply to impurities. An impurity is a substance not intentionally added to a product. Instead, it is either a byproduct of the manufacturing process, formed by the breakdown of ingredients, or an environmental contaminant of raw ingredients. Many of the restricted chemicals are not prohibited in the US. Also, cosmetic makers must register their products and report cosmetic components and the concentration of each. Since November, 2006, Canada has required product ingredient lists to be visible on all personal care product labels.

**US Labeling Laws and Evidence of Unlabeled Toxins**

The Federal Fair Packaging and Labeling Act was passed in 1973 to require cosmetic ingredient labeling, but significant exceptions were made. According to the Act, flavor, fragrance and trade secret ingredients are not required to be included on the label (FDA, 1991). This loophole in the FDA cosmetics labeling law allows prominent ingredients, including toxic chemicals, to be left off the label. The Federal Trade Commission (FTC) can take legal action if it discovers that companies are making false advertising claims. Many terms commonly used on the label have no legal definition and prevent the FTC from taking action. Marketing terms such as natural, pure, hypoallergenic and organic do not have any enforceable legal definition related to cosmetics. According to the FDA, these terms are defined by the cosmetic seller labeling the product. Rastogi (1996) found that 82% of perfumes based on “natural ingredients” contain synthetic fragrances. Several studies have found that many chemical ingredients
are not on the label. Sarantis et al. (2010) tested 17 fragrance products and found 38 of 40 chemical ingredients unlabeled. Among the unlabeled chemicals was diethyl phthalate. Four of the unlabeled chemicals include substances required to be labeled by the European Union. EWG reports that 6 of the chemicals are potential endocrine disruptors, nine are potential sensitizers or contact allergens, and 10 of the chemicals do not have any toxicity data in Pubmed. There is limited data for most of the unlabeled substances because few or no toxicity studies are available. A large portion of the information that is available indicates that there is a reasonable cause for concern and a need for further studies.

Under the FD&C Act, cosmetic firms are required to list the intended ingredients in products. Unintentional ingredients such as phthalates or lead are not required to be labeled because they are considered unintended impurities or by-products of the manufacturing process. FD&C Act is authorized by the FDA, but according to the FDA, it is the cosmetic firm’s responsibility to make sure the products are safe and properly labeled. Cosmetic manufacturers and suppliers are not required to register with the FDA or give the FDA information on ingredients or cosmetic-related injuries.
Nursing Implications

Nurses can promote exposure prevention through education, assessment, treatment and policy advocacy. Health care professionals are in a unique position to teach the population and individual patients about the hazards of phthalates, parabens and lead. With the educational foundation to access and interpret scientific studies and the nature of the professional title, the provider can influence legislation, educate the public in a systematic way and meet directly with the individual.

Patient Teaching

Education and awareness are the first steps in protecting the public from adverse health effects from chemicals in personal care products. The public is largely unaware of the lack of government protection and the hazards related to personal care products. Even when consumers are made aware of the risks and have a desire to change, lack of labeling requirements and availability of safe and affordable products are major barriers. Buying products based on labels is not enough to ensure safety. For example, regulations allow the manufacturer to label a product as “fragrance-free” if the fragrance material has more than one function, such as a preservative or emollient. Therefore, “fragrance-free” does not mean that the product does not contain a fragrance (Scheinman, 2000; Steinemann, 2009). Even if ingredients are derived from a plant or animal source, they still may not be safe. (Scheinman, 2000). Parabens, lead and phthalates represent only a small portion of undisclosed toxins found in personal care products. Many of these undisclosed
ingredients are known to cause harm and have the propensity to accumulate in human tissue which increases the potential for adverse effects. Most cosmetic ingredients have not been assessed for safety. According to Caress and Steinemann, (2009), a growing number of people report adverse reactions to scented products from several exposure mediums including contact with products worn by others, products displayed in stores, from air fresheners and from household products. Encouraging patients to report adverse side effects of personal care products can increase professional and individual awareness and provide information needed for active policy development. Even if all the ingredients are included on the label, the average consumer does not have the fundamental background in chemistry to make informed decisions about which products are safe.

Despite the barriers to safe product use, nurses can still address exposure prevention by educating the public about potential adverse effects, incident reporting, safe product resources, decreased product use, and local and national environmental organizations that support prevention. Personal care product chemical exposure education can be incorporated into routine health care visits. A structured exposure assessment form is an efficient way to evaluate possible exposure and stimulate questions. Women of childbearing are in contact with nurses more frequently for pre-conception and prenatal care. This face to face contact provides an opportunity to discuss exposure prevention and increased vulnerability to chemicals during rapid development. Possible education strategies beyond the bedside include professional presentations, informational posters and publications. Further dissemination of environmental hazard risks can be accomplished by educating other providers and improving collaboration between
providers and agencies. Knowledge is an essential tool for citizens to address environmental health issues.

Teen years represent a vulnerable life stage in relation to toxic cosmetics for several reasons. First, it is a period of physical development and the body is therefore more vulnerable to the effects of toxins at a lower dose. Second, teen puberty causes body odor and skin eruptions from glandular and hormonal disturbances can lead to emotional struggle and embarrassment. Teenagers, seeking independence, are likely to experiment with a wide variety of available personal care products without talking to an adult or healthcare provider. Peer influence, preoccupation with appearance and oppressive beauty standards encourage teens to use large amounts of cosmetics. Educating teens and parents to choose nontoxic body care products and to accept body changes as a normal part of development will promote health decisions while coping with this life stage.

Nurses can help patients find safe and affordable alternatives. This requires the provider to be educated about safe options, which is challenging. Most off-the-shelf products rely on synthetic chemicals for preservation, color, fragrance and for bulking, so there are few truly safe options. Providing trusted resources allows consumers to evaluate individual products and make informed decisions. Since 2000, EWG has been researching the safety of personal care product ingredients and the laws that govern them. Based on their research, they publish public information on the Skin Deep website. Skin Deep is a searchable public online database that educates the consumer about the safety of ingredients in over 29,000 personal care products. Skin Deep also provides a list of
certified organic products. EWG has printable pocket-sized shopping guide for consumers to take with them to makeup counters or drug stores. The Campaign for Safe Cosmetics is another nonprofit organization that provides cosmetic information to the public. One simple way to decrease toxic exposure is to use fewer products. Helping patients to make decisions about which products can be replaced and which products can be eliminated will promote future health and public awareness.

Time constraints do provide limitations for the provider. Therefore encouraging the public, once educated about the risks, to educate one another will increase general public awareness. Role modeling, openly discussing this topic in day to day life, and promoting precautionary legislation related to the lack of safety surrounding the use of personal care products under current US policy will promote public knowledge and public safety.

**Identifying and Treating Exposures**

Consideration for toxic exposure from personal care products can be incorporated into the nursing assessment and should be considered in the formation of differential diagnoses.

When assessing the patient for exposures, it’s relevant to consider trends in body burden and presenting symptoms. Due to regulations, there has been a decrease in lead exposure and therefore current clinical presentation is generally chronic and subclinical. It’s challenging to measure subtle cognitive changes and the tools to measure lead levels are insensitive when assessing exposure. Likewise, clinical presentation of phthalate and paraben exposure is often subclinical and the adverse effects can be related to a number
of conditions or exposures. The initial response to identified exposure is removing the patient from the source of exposure followed by correction of body burden if possible.

**Advocacy**

Although patients can limit exposure by paying attention to products they purchase, to a large extent the exposure comes from sources beyond their control. Nurse advocacy of active policy development of cosmetic ingredients has the potential for a much broader impact than individual prevention. Professional membership in nursing organizations, such as the American Nurses Association, provides a forum for nurses to join voices and make professional statements in support of safe cosmetic policy. Nursing programs in the U.S. historically lack sufficient environmental health education, but international recognition of environmental hazards is increasing the incorporation of this content into nursing curriculums. When nurses are educated on current regulations and environmental health risks they are better equipped to get involved in policy development. Advocating for cosmetic legislation that exposes hazardous products and aims to prevent the use of toxins in personal care products protects consumer health. Cosmetic legislation affects every American who uses moisturizer, shampoo or deodorant. More and more people are concerned about unsafe chemicals in our everyday lives. There are broad environmental health consequences associated with continual introduction of cosmetic toxins into sewage treatment systems and directly into recreational waters from human skin. This contamination of water supplies has the potential for wide-spread environmental impacts. The individual citizen has the right to voice their opinion about government policy and lobby for government involvement and
FDA regulation. Encouraging consumers to talk to their legislators and congressmen about safety concerns will promote policy change to regulate the safety of products sold in the US. Consumers may assume that the government ensures safety by regulating cosmetics the same way it does food and drugs and nurses can help overcome these public misconceptions. The history of secrecy within the cosmetic industry has created a culture of ignorance around personal care products. The regulation of cosmetics has not been updated since 1938.

Policy makers want compelling evidence to drive regulatory decisions. Regulations related to chemical exposure are often out of date because the analysis of studies may be 10 years late. This lag in analysis causes the evidence that drives cosmetic regulations to be inadequate. For example, lead was found in paint in 1908, but the US did not remove lead from paint until 1976, long after other countries already had. Also, there is a misconception that the lead problem is solved because lead levels are decreasing, but in reality almost everyone has some level of lead burden. Current research has shown adverse effects with levels far below the current action level. Compelling data is not always available for policy makers, in part because it may be unethical to collect hard data. For example, it would be unethical to intentionally give potentially hazardous cosmetic ingredients to study subjects so some studies can’t morally be conducted. In 1992, the precautionary principle was defined at the Rio Conference, an international environmental health convention. According to the precautionary principle, in the presence of threats with serious and irreversible damage, the lack of full scientific certainty shall not be used as reason to postpone cost effective
measures to prevent environmental degradation. The precautionary principle has historically not been upheld in the cosmetic world and there are related health consequences. Studies show an increase in incidence of health outcomes related to lead, phthalates and parabens. Nurses can consider the precautionary approach when promoting safe regulations and educating patients.

The power of the cosmetic industry has a major impact on regulatory decisions, but the industry is bias due to a fiscal commitment to shareholders. Historically, the cosmetic industry has been able to prevent politicians from publishing EPA studies regarding personal care product toxins due to inadequate evidence. Financial resources are a powerful tool used to collect information and organize key players needed to present a sound case for advocacy of political movement. Body burden of lead, phthalates and parabens often have subclinical effects. The public is more willing to recognize and financially support more visible medical conditions, such as asthma. Nurses can promote needed financial support to decrease environmental hazards. Participation in professional organizations that address personal care product exposures and collaboration between health care workers strengthens efforts to build needed financial resources to advocate for public safety.

Nurses are role models and can impact others perceptions and decisions by simply avoiding environmental exposure personally and discussing these actions with the public. By purchasing safe products, consumers indicate to manufacturers that there is a demand for safe products. General conversation about personal care product regulation and safety with friends, community members and colleagues increases public awareness and drives
positive change. A significant impact on the detrimental effects of environmental health hazards and adverse health effects will only occur with a joint effort from multiple parties. Nurses advocate policy development and educate the public to promote this positive global impact.

**Conclusion**

Research indicates an association between the use of personal care products and adverse health outcomes. Phthalates, parabens and lead represent a small number of the many industrial chemicals detected in most cosmetics manufactured and sold in the United States. Personal care product use exposes humans to chemicals through dermal absorption, inhalation and unintended ingestion. Phthalates, parabens and lead accumulate in the body and studies show that almost all U.S. residents have some level of body burden. Epidemiology of health outcomes shows an increasing trend in some negative health effects associated with phthalates, parabens and lead. The U.S. government does not review the safety of ingredients and contaminants in personal care products. Instead, FDA regulation legally requires the cosmetic industry to evaluate personal care products safety. The cosmetic industry is responsible for both the interests of its shareholders and for the safety of its products.
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APPENDIX A

CHEMICALS FOUND IN PERSONAL CARE PRODUCTS

AND ASSOCIATED HEALTH EFFECTS
Table 1: Studies Showing Associations Between Phthalates and Adverse Health Effects

<table>
<thead>
<tr>
<th>Phthalates</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>Swan (2008); Okubo, Suzuki, Yokoyama, Kano, &amp; Kano (2003)</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Cobellis et al. (2003); Reddy, Rozati, &amp; Raman (2006); Swan (2008)</td>
</tr>
<tr>
<td>Impaired fertility</td>
<td>Lamb IV, Chapin, Teague, Davis Lawton, &amp; Reel (1987); Swan (2008)</td>
</tr>
<tr>
<td>Preterm Birth/LBW</td>
<td>Swan (2010); Swan (2008)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Hatch et al. (2008); Stahlhut, Van Wijngaarden, Dye, Cook, &amp; Swan (2007)</td>
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<tr>
<td>Hypothyroidism</td>
<td>Huang, Kuo, Guo, Liao, &amp; Lee (2007); Schreder (2009)</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>Diamanti-Kandarakis (2009); Ormond et al. (2009)</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>Swan 2008 &amp; 2010</td>
</tr>
<tr>
<td>Reduced sperm count</td>
<td>Diamanti-Kandarakis (2009); Duty et al. (2004); Hauser et al. (2007)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Stahlhut, Van Wijngaarden, Dye, Cook, &amp; Swan (2007)</td>
</tr>
<tr>
<td>Reduced sperm quality</td>
<td>Duty et al. (2004); Hauser et al. (2007); Hauser, Meeker, Duty, Silva, &amp; Calafat, (2006)</td>
</tr>
<tr>
<td>Male reproductive problems</td>
<td>Duty et al. (2004); Hauser et al. (2007); Hauser, Meeker, Duty, Silva, &amp; Calafat, (2006)</td>
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<tr>
<td>reduced anogenital distance</td>
<td>Marsee, Woodruff, Axelrad, Calafat, &amp; Swan (2006); Swan et al. (2005)</td>
</tr>
<tr>
<td>Asthma</td>
<td>Bornehag et al. (2004); Wormuth, Scheringer, Vollenweider &amp; Hungerbühler (2006)</td>
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<tr>
<td>Dermal effects</td>
<td>RIMF (1978); Wormuth, Scheringer, Vollenweider &amp; Hungerbühler (2006)</td>
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<tr>
<td>Increase liver and kidney weight</td>
<td>Brown, Butterworth, Gaunt, Grasso, &amp; Gangolli (1978)</td>
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<tr>
<td>Increased liver function tests</td>
<td>Mapuskar, Pereira &amp; Rao (2007)</td>
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<tr>
<td>Testicular Cancer</td>
<td>Diamanti-Kandarakis (2009);</td>
</tr>
<tr>
<td>Feminization of males</td>
<td>Swan (2010); Swan (2008)</td>
</tr>
<tr>
<td>Smaller penis</td>
<td>Swan (2010); Swan (2008)</td>
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<tr>
<td>Premature puberty</td>
<td>Colón, Caro, Bourdony, &amp; Rosario, (2000); Swan 2008</td>
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Table 2: Studies Showing Associations Between Parabens and Adverse Health Effects

<table>
<thead>
<tr>
<th>Parabens</th>
<th>References</th>
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<tr>
<td>Breast Cancer</td>
<td>Darbre &amp; Harvey (2008); Ishiwatari et al. (2007)</td>
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<tr>
<td>Preterm Birth/LBW</td>
<td>Ge &amp; Chang (2006)</td>
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<tr>
<td>Obesity</td>
<td>Hu et al. (2013)</td>
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<td>Reduced sperm count</td>
<td>Ge &amp; Chang (2006)</td>
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<tr>
<td>Reduced sperm quality</td>
<td>Ge &amp; Chang (2006)</td>
</tr>
<tr>
<td>Uterotrophic effects in vivo</td>
<td>Ge &amp; Chang (2006)</td>
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<tr>
<td>Allergenic sensitization</td>
<td>Savage, Matsui, Wood, &amp; Keet (2012)</td>
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<tr>
<td>Testosterone inhibition</td>
<td>Chen et al. (2007)</td>
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Table 3: Studies Showing Associations Between Lead and Adverse Health Effects

<table>
<thead>
<tr>
<th>Lead</th>
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<tbody>
<tr>
<td>Preterm Birth/LBW</td>
<td>IPCS (1995)</td>
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<tr>
<td>ADHD</td>
<td>Braun, Froehlich, Kahn, Auinger, &amp; Lanphear (2006)</td>
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<tr>
<td>Premature puberty</td>
<td>Selevan (2003)</td>
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<tr>
<td>Decreased IQ</td>
<td>Canfield (2003); Fewtrell, Kaufmann, Pruss-Ustun, (2003); Lanphear (2005)</td>
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<tr>
<td>Decreased mental dev. Index</td>
<td>Tellez-Rojo (2006)</td>
</tr>
<tr>
<td>Decreased psychomotor dev index</td>
<td>Tellez-Rojo (2006)</td>
</tr>
<tr>
<td>Decreased height</td>
<td>World Health Organization &amp; Ebrary (2009)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Cave (2010)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Aykin-Burns, Laegeler, Kellogg &amp; Ercal (2003); Mudipalli (2007)</td>
</tr>
<tr>
<td>Decreased Infant dev scores</td>
<td>Bellinger, Leviton, Waternaux, Needleman, &amp; Rabinowitz (1987)</td>
</tr>
<tr>
<td>Miscarriage/Stillbirth</td>
<td>IPCS (1995)</td>
</tr>
<tr>
<td>Fetal malformations</td>
<td>IPCS (1995)</td>
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