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The effect of chemical fragrances on child health and development

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THE EFFECT OF CHEMICAL FRAGRANCES ON CHILD HEALTH AND DEVELOPMENT

by

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Abstract

The American public is bombarded with chemically fragranced products every day, typically in combination with each other. These products can include cosmetics, perfumes, detergents, air fresheners, soaps, and deodorants. Contained in these fragranced products are chemicals that can be harmful to child health and development. Many articles have been published examining the chemicals found in fragranced products and the effects that these chemicals can have on the human body. This integrated literature review examines empirical evidence related to the health and safety of particular chemicals used in these products. Nurses need to be aware of the actual and potential harms from the chemicals used in the self-regulating cosmetic industry and can advocate for public policies that promote a safer environment, therefore protecting the health and wellbeing of children.

Dedications

In memory of my mother, who dedicated her life to teaching children and pushed me to always strive for the best.

To my father, whose research along the years has inspired me to write this thesis.

To Libby, for all of your encouraging words.

To Robert, for all the love and support you give.

And to everyone else who has had a positive impact on my life, I thank all of you.

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Introduction

As it stands today, cosmetic manufacturers can include potentially harmful chemicals in many products found inside the household without the knowledge of the public. The Fair Packaging and Labeling Act created a loophole for companies to withhold knowledge of the presence of certain chemicals from the public by using the term “fragrance” in the ingredient list without disclosing all of the chemicals used in the product. Many of these chemicals have not been adequately tested for safety before being marketed. Certain chemicals have been banned in the formulations of fragrances in other countries, but the United States has yet to do so.

Background

The United States Food and Drug Administration (FDA) regulates the food supply and ensures the safety and effectiveness of drugs and medicines for the American public. Cosmetics are regulated by the FDA's Center for Food Safety and Applied Nutrition (CFSAN). One of CFSAN's responsibilities is to regulate the safety of cosmetic ingredients and ensure that the cosmetics are properly labeled. The FDA approves the safety of color additives used in cosmetics, but is not responsible for testing the safety of all the chemicals found in personal care products. In fact, it is the responsibility of the cosmetic manufacturer to ensure the safety of the products before marketing them to the general public (FDA, 2011).

The Federal Trade Commission (FTC) was created to "protect America's consumers" (FTC, 2011). That being said, the FTC's Fair Packaging and Labeling Act states that companies must list "the common name of each ingredient (on the label), but nothing in this (Act) shall be deemed to require that any trade secret be divulged" (FTC, 2011). This "loophole" makes it possible for companies to conceal chemicals in household products by using the term "fragrance" in the ingredient list to hide their formula from other companies.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) prohibits selling adulterated or misbranded products to the American public. Adulterated products are defined as any product that "bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof" (FDA, 2011). This means that toxic chemicals should not be used in formulating cosmetics, but due to a lack of regulation, companies can keep the public uninformed about harmful chemicals in their products by classifying them as part of the "fragrance".

The endocrine system is composed of glands and glandular tissues that communicate with the body by producing, storing, and secreting hormones that travel through the blood to target cells in the body (Lewis, Heitkemper, Dirksen, O'Brien, & Bucher, 2007). It is responsible for energy levels, reproduction, and growth and development. Endocrine disruptors are "naturally occurring compounds or man-made chemicals that may interfere with the production or activity of hormones of the endocrine system leading to adverse health effects" (NIEHS, 2006). Endocrine disruptors act in three ways to interfere with the body's natural hormone functions. The disruptors can mimic naturally occurring hormones in the body, leading to overstimulation of the hormone due to the similarity to the natural hormone. They can also block the transportation of the natural hormone by binding to receptors in the cell, ceasing communication with the receptor, which, in the absence of stimulation, causes the body to respond improperly. Lastly, endocrine disruptors can interfere or block the way that natural hormones are made or controlled (NIEHS, 2006).

Phthalates are a well known example of endocrine disruptors that can be found in many household items such as cosmetics, perfumes, soaps, shampoos, lotions, deodorants, aerosols, shower curtains, and children's toys (Engel et al., 2010). Diethyl phthalate (DEP) has been found in more than 97% of the United States population (Silva et al., 2004). DEP has been associated with abnormal reproductive organ development in boys and decreased sperm count in men (Sarantis, Naidenko, Gray, & Houlihan, 2010). Recent studies also indicated that phthalates are negatively associated with thyroid function (Boas et al., 2010) and linked prenatal phthalate exposure to Attention Deficit Disorder in children (Engel et al., 2010). High molecular weight phthalates act as plasticizers, which soften the plastic to make it more flexible. Low molecular

weight phthalates are more commonly found in personal care products (Engel et al., 2010). The low molecular weight phthalates are used in hairspray to allow the spray to become pliable, in nail polish to help resist chipping, and in fragrances to make the scent linger. Prenatal phthalate exposures have been associated with "reduced testosterone production in fetal testes, incomplete development of the male reproductive tract and malformations of the external genitalia" (Marsee et al., 2006). Phthalate exposures have also been associated with preterm birth, which causes more than one million neonatal deaths globally and more than one-third of all infant deaths in the United States (Meeker et al., 2009).

The FDA's role in regulating cosmetics is limited to approving the color additives used in chemically fragranced products and has no other legal authority over the cosmetic industry. According to the FDA, a "change in FDA's statutory authority over cosmetics would require Congress to change the law" (FDA, 2011). The Cosmetic Ingredient Review (CIR) was established in 1976 to "thoroughly review and assess the safety of ingredients used in cosmetics in an open, unbiased, and expert manner, and publish the results in the peer-reviewed scientific literature" (CIR, 2011). Since 1976, the CIR has only established 9 chemicals as "unsafe" for use in cosmetics and currently lists 51 chemicals which have "insufficient data" to support their safety. Another 51 chemicals have been listed as "zero use ingredients with insufficient data." These ingredients are no longer reported to be used to the U.S. FDA's Voluntary Cosmetic Registration Program (VCRP) (CIR, 2011). The VCRP is a voluntary reporting system that cosmetic companies can opt to participate in. Cosmetic ingredients are disclosed to the VCRP who then reports to the FDA and CIR. If an ingredient is found to be harmful, the FDA will notify the companies registered with VCRP. Because companies are not required to register with

the VCRP and report their ingredients, the "zero use" chemicals with insufficient data will not be tested for safety (FDA, 2011).

The International Fragrance Association (IFRA) was founded in 1973 and is another voluntary regulatory program for the fragrance industry. The IFRA develops a Code of Practice based on assessments carried out by an Expert Panel of professionals from the fields of dermatology, toxicology, pathology, and environmental sciences. Their role is to evaluate the data on a fragrance to make sure there is no risk for the consumer. If the safety information does not support current use, the Expert Panel instructs IFRA to either restrict or ban the chemical. Membership is open to fragrance manufacturers from all countries, but is not mandatory (IFRA, 2011).

Contact allergy to fragranced products is a well-recognized problem. It has been estimated that 2-4% of the general population suffers from a contact allergy to fragrances (Schnuch et al., 2007). In 2007, the American Contact Dermatitis Society named fragrance the "Allergen of the Year" (American Contact Dermatitis Society, 2011). Respiratory illnesses are the most common causes of sickness and hospitalization in children (Ricci & Kyle, 2009). Sensitizers, which can cause allergic responses such as asthma, wheezing, headaches, and contact dermatitis, are found in many chemically fragranced products. According to the Occupational Safety and Health Administration (OSHA), a sensitizer is "a chemical that causes a substantial proportion of exposed people or animals to develop an allergic reaction in normal tissue after repeated exposure to the chemical" (United States Department of Labor, 2011). Repeated, cumulative exposure to chemical sensitizers like those found in chemical fragrances

increases the chance that a person will develop allergic symptoms later in life (Sarantis, Naidenko, Gray, & Houlihan, 2010).

Commonly used sensitizers used in fragranced products were identified in studies performed by the Environmental Working Group and the United Kingdom. Isoeugenol, a commonly used sensitizer, has a sweet, spicy, floral odor and is restricted in formulations to 0.02% in the European Nations. However, the incidence of allergy to isoeugenol has increased since 2002 in European patch test patients. An explanation for this could be an increase in the frequency of use, creating a higher concentration that is absorbed or inhaled. Geraniol smells sweet and has an odor similar to a rose. It is one of the most commonly used fragrances in household and cosmetic items. In soap for handwashing, geraniol has been associated with hand eczema. Linalool is a floral woody odor combined with a faint citrus smell (Buckley, 2007). It is a very widely used chemical sensitizer and oxidizes upon exposure to the air. These oxidation products have been known to cause contact allergies (Schnuch et al., 2007).

According to the U.S. Agency for Toxic Substances and Disease Registry, "The effects of exposure to any hazardous substance depend on the dose, the duration, how you are exposed, personal traits and habits, and whether other chemicals are present" (ATSDR, 2011). Typically, humans are not just exposed to one fragrance, but multiple fragrances at one time. Fragrances are designed to linger in our homes, on our bodies, and on our clothing throughout the day. Many chemicals have not been adequately tested for safety before marketing, and those that have been tested are simplistic and do not take into consideration chemical interactions.

Currently, the European nations ban diethyhexyl phthalate (DEHP), dibutyl phthalate (DBP), and benzyl butyl phthalate (BBP) in excess of 0.1% by mass of the plasticized toy or

childcare article. The European nations also ban di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP), and di-n-octylphthalate (DNOP) in excess of 0.1% by mass of plasticized parts of toys that can be placed in the mouth. These phthalates were banned due to scientific studies linking them with reproductive and hormonal changes (Directive 2005/84/EC, 2005). In 2004, the European Parliament banned many chemicals that are classified as carcinogenic, mutagenic, or toxic from cosmetic products. Of those, DBP, DEHP, and dimethoxyethyl phthalate (DMEP) were listed and were banned from production (Directive 2004/93/EC, 2004). In the United States, DEHP, DBP, and BBP are regulated for reducing childhood exposure, specifically in plastic bath and play toys that can easily be put in the mouth of a small child. Currently, the FDA "does not have compelling evidence that phthalates, used in cosmetics, pose a safety risk" (FDA, 2011). Although the European nations have recognized phthalates as harmful and banned them from plastic toys as well as cosmetics, the United States fails to regulate them in products other than children's toys.

Problem

A one-time use of chemicals like these may not cause harm to the human body. However, the chemicals in fragrances, such as phthalates, are used repeatedly and often in combination with other chemicals within the household creating a greater risk for chemical exposure and toxicity. The chemicals may be inhaled directly from the air through aerosols or absorbed through the skin by detergents and perfumes. Phthalate diesters are excreted from the body within a couple of days, with most of the dose cleared within 24 hours. In a 2006 study performed on maternal phthalate exposures, nearly all of the subjects had detectable amounts of phthalates in their urine indicating a continuous daily exposure (Marsee et al., 2006). Consistent

use of products containing phthalates during pregnancy has shown environmental exposure biomarkers, whereas sporadic use of phthalate containing products show more variability (Wolff et al., 2008).

Pregnant women, fetuses, and newborns are more vulnerable and highly sensitive to the effects of toxic chemicals (Hogberg et al., 2008). Fetuses are especially susceptible to develop cognitive or developmental disparities because they receive higher doses of chemicals relative to their body weight (Phillips, 2005). Children are also more heavily exposed to these toxins due to their decreased body weight and continuous chemical exposure. Because these chemicals are not regulated in these products and many parents and adults are not informed about the harmful effects of chemicals in the fragrance of many products, children are continuously being put at risk for developing cognitive and physiological issues later in life.

Purpose

The purpose of this integrated research review is to identify the effects of phthalates and sensitizers on fetal, infant, and child development and the risk of developing health related abnormalities and problems later in life. Based on the evidence about the known and potential harms of the chemicals used in fragranced household products, appropriate actions for nurses to engage in, including patient advocacy and teaching, are identified.

Method

An exhaustive search of the literature was done using the databases CINAHL and MEDLINE. Search terms included "phthalate, musk, fragrance, health, allergy, development, perfume, air freshener, aerosol, pregnancy, and children". All research articles were written in English and peer reviewed. To supplement the articles found via the database search,

government and independent organizations' publications were included. To find these organizations, Google search was used. Search terms included "Environmental Working Group, Campaign for Safe Cosmetics, Food and Drug Administration, Europe, phthalate, and regulation". Due to a limited amount of research funded and peer reviewed in the United States and disagreement among countries regarding the safety of phthalates, articles were included from any country. The research articles included information on reproduction or child health and development. Any article that had been published within the last 10 years meeting these criteria was included.

Findings

A total number of twelve studies were identified that met the inclusion and exclusion criteria. Ten of these studies were peer reviewed and two were conducted by private organizations. Four studies were performed in the United States and eight were performed in other countries, including Italy, Mexico, Denmark, South Korea, Sweden, China, Finland, Bulgaria, and the United Kingdom.

Hidden Ingredients

In a study performed by the Environmental Working Group and the Campaign for Safe Cosmetics, 38 chemicals not listed on the label were found in 17 name brand perfumes (Sarantis, Naidenko, Gray, & Houlihan, 2010). Of those 38 chemicals, 10 of them lack any published safety information and 6 chemicals have three or fewer published toxicity studies in scientific journals. Among the 38 unlisted chemicals were sensitizers, endocrine disruptors, and known carcinogens.

Another study performed in the United States analyzed 25 fragranced consumer products and found 133 different volatile organic compounds (VOCs) within the products. Twenty four of the VOCs are classified as toxic or hazardous under U.S. Federal laws, including the Clean Air Act; Comprehensive Environmental Response, Compensation, and Liability Act; Emergency Planning and Community Right-to-Know Act; Federal Insecticide, Fungicide, and Rodenticide Act; Occupational Safety and Health Act; and the Resource Conservation and Recovery Act. Each of the 25 products contained at least one toxic compound. The study tested four laundry products, nine personal care products, four cleaning supplies, and eight air fresheners. The products were selected based on popularity of use and each product ranked in the top of their

categories for consumer sales. Of the 133 VOCs, only one, ethanol, was listed on the ingredient label, and two of the compounds were identified on a material safety data sheet- ethanol and 2-butoxyethanol. The rest of the 132 VOCs have been included as part of the "fragrance" (Steinemann et al., 2010).

Phthalates

In a multi-ethnic birth cohort study performed on 295 neonates at the Mount Sinai School of Medicine in New York City, a correlation was found between the level of phthalate metabolites and the results of the Brazelton Neonatal Behavioral Assessment Scale (NBAS). The NBAS is designed to assess the newborn's behavior to regulate its internal state as well as interactions with the environment. The assessment contains 8 categories: habituation, social-interactive, motor, state organization, state regulation, autonomic system, supplementary items, and reflexes (Hawthorne, 2005). In the Mount Sinai study, the NBAS was administered to the neonates within 5 days of delivery. Maternal urine was collected between 25 and 40 weeks of gestation and phthalate metabolites were measured. A relationship was found between increased maternal phthalate concentrations and decreased scores in mean orientation ($p<0.02$) and overall alertness ($p<0.01$) of female neonates (Engel et al., 2009).

A subsequent study was then performed on 188 of those children who returned one to three times for follow-up visits between four and nine years of age. At each visit, the mothers would complete the Behavior Rating Inventory of Executive Function (BRIEF). This 86 item questionnaire is designed to assess executive cognitive function in children between the ages of 5-18 years of age. The BRIEF is composed of eight categories: inhibition, shifting, emotional control, initiation, working memory, planning/organization, organization of materials, and

monitoring (Engel et al., 2010). Parents were also asked to fill out the Behavior Assessment System for Children-Parenting Rating Scales (BASC-PRS). The BASC is composed of 130 items and is designed to evaluate problematic behaviors in children between the ages of 2.5-18 years of age. Levels of high molecular weight phthalates were not associated with a correlation of the BRIEF and BASC scores. However, a statistically significant correlation was found between increased levels of low molecular weight phthalates (LMWP) and decreased behavioral and executive functioning profiles of the children as reported by the BRIEF and BASC. More specifically, children of higher LMWP concentrations showed higher scores in the categories of aggression ($p<0.02$), conduct problems ($p<0.02$), hyperactivity ($p<0.04$), and externalizing problems ($p<0.01$). A less statistically significant correlation was found between attention problems ($p<0.16$), depression ($p<0.19$), social skills ($p<0.14$), and adaptive skills ($p<0.12$) (Engel et al., 2010).

A cross-sectional study examining the relationship between urinary concentrations of phthalate metabolites and children's intellectual functioning was performed on 621 fourth, fifth, and sixth grade children at nine Elementary schools in South Korea. The children were individually administered the Korean Educational Developmental Institute-Wechsler Intelligence Scale for Children (KEDI-WISC) which consists of vocabulary, arithmetic, picture arrangement, and block design tests. The sums of the age adjusted scores for vocabulary and arithmetic were used to estimate Verbal IQ and the sums for picture arrangement and block design were used to estimate Performance IQ. The examiners administered the Korean Wechsler Adult Intelligence Scale (KWAIS) to the children's mothers. Similarly to the KEDI-WISC, the exam also estimated a Verbal IQ and Performance IQ using the same categories. The children's urine was collected in

paper cups where phthalate metabolites were measured using high performance liquid chromatography tandem mass spectrometry. To control for dilution, the urine concentrations were creatinine corrected. A higher level of MEHP was associated with a decrease in the Full Scale IQ ($p<0.01$), Verbal IQ ($p<0.01$), vocabulary ($p<0.001$), and block design ($p<0.05$). Increased levels of MEOHP correlated with a decreased Full Scale IQ ($p<0.05$), Verbal IQ ($p<0.01$), vocabulary ($p<0.001$), and block design ($p<0.05$). Higher levels of MBP were found to negatively affect the vocabulary and block design scores ($p<0.05$). After correcting for age, sex, birth weight, history of breast feeding, residential area, paternal education, and maternal IQ, only the vocabulary scores remained statistically significant, with a p value of 0.01 for MEHP and 0.015 for MEOHP (Cho et al., 2010).

An Italian cohort study linked preterm birth with increased levels of di-ethylhexyl phthalate (DEHP) or its metabolite, mono-ethylhexyl phthalate (MEHP). In this study, cord blood samples were collected from 84 newborns at the Brindisi Hospital in Italy. The maternal age at delivery ranged from 18-42 years old and the sample contained 39 male and 45 female infants. Blood specimens were obtained directly after delivery, using only glass devices to rule out phthalate contamination from plasticizers in the medical equipment. DEHP, MEHP, or both were found in 74 out of 84 cord blood samples. The newborns who were MEHP positive showed a significantly lower gestational age compared to MEHP negative infants ($p=0.033$) (Latini et al., 2003).

Similarly, in a Mexican birth cohort study performed in Mexico City, increased levels of several phthalate metabolites were associated with preterm birth. Women were recruited during prenatal visits at the Mexican Institute of Social Security clinic. The women that were eligible

did not present with a high-risk pregnancy, including denying daily consumption of alcoholic beverages, addiction to illegal drugs, continuous use of prescription drugs, or a diagnosis of a medical condition such as preeclampsia, renal or heart disease, or gestational diabetes. Of the eligible women, 518 of them were tested for urinary metabolites in their third trimester. Forty-four women delivered before 37 weeks gestation and 30 of them were randomly selected along with thirty controls who delivered after 37 weeks of gestation. The urine samples of the women who delivered at term were more dilute then those that delivered preterm. The phthalate metabolites were measured before correction for dilution and after correction by specific gravity and creatinine. Eighty percent of the concentrations of phthalate metabolites in preterm deliveries before correction were higher than those of the control group. The largest difference in uncorrected phthalate metabolites was found in MBP, where the average concentrations of preterm urine samples was three times higher than the controls. Uncorrected, MBP had a p value of <0.005, and corrected by specific gravity and creatinine had a p value of <0.01 (Meeker et al., 2009).

Another study associating preterm birth with maternal phthalate exposure was performed on Chinese newborns in 2005-2006. The nested case-control study initially recruited 125 mothers who delivered low birth weight (LBW) babies and 125 controls at the Shanghai Medical Center for Maternal and Child Health. After excluding multiple birth pregnancies or premature deliveries, the sample size fell to 201 pairs; 88 LBW newborns $\geq$37 weeks gestation and $<$2500g along with 113 control babies $\geq$37 weeks gestation and $>$2500g. Umbilical vein blood was obtained from all 201 babies immediately after delivery, and maternal blood was taken after the mothers completed a survey. Meconium was collected within 48 hours of delivery and stored in

phthalate-free containers in freezing temperatures at Fudan University pending analysis. Three phthalates (DEP, DBP, and DEHP) and their metabolites (MBP and MEHP) were analyzed from the cord blood and meconium samples. The phthalate concentrations remained constant in the cord blood, maternal blood, and neonatal meconium.

The percentage of phthalate concentration greater than the level of detection (LOD) was significantly higher in the LBW infants than the control group. In the maternal blood, the percentage above the LOD for DEP was 79.4% in the control group, as opposed to 94.3% in the LBW group. The percentage of DBP was 82.9% higher than the LOD in the control group and 92.9% for the LBW infants. For DEHP, the control group had a percentage of 72.3% above the LOD in controls and 84.3% in LWB infants. Likewise, for MEHP, the control group had an 80.1% increase of the LOD and the LBW group had an 88.6% increase. In the cord blood, the percentage of DEP was 76.1% in the control group and 96.6% in LBW infants. For DBP, the control group had a percentage above the LOD of 74.8% and the LBW group had a percentage of 97.7%. DEHP had a percentage of 67.3% for the control group and 77.1% for the LBW infants. MEHP showed a lower percentage in the control group than the LBW group, with 71.4% for controls and 85.2% with the LBW group. The neonatal meconium showed the same correlations. In MBP, the percentage above the LOD for the control group was 74.3% as opposed to 95.5% in the LBW group. MEHP had a percentage of 76.1% for the controls and 87.5% for the LBW infants. Statistically significant correlations with DBP and low birth weight were found in the maternal blood ($p<0.02$) and cord blood ($p<0.002$). Increased levels of maternal MBP correlated with low birth weight in neonatal meconium ($p<0.003$). Similarly, the study found a relationship

between MEHP and low birth weight in maternal blood, cord blood, and meconium with a p value of <0.000 for all samples (Zhang et al., 2009).

Phthalates have also been associated with decreased anogenital distance (AGD) in male infants (the distance from the center of the anus to the posterior base of the scrotum). This cohort study measured the anogenital index (AGI), which was calculated by the AGD divided by the boys' weight. The study tested prenatal urine for phthalate metabolites in 85 women pregnant with male fetuses, and later examined the boys' AGD at a mean age of 15.9 months old. The boys' AGIs were then plotted based on the expected AGI and its 25^{th} and 75^{th} percentiles. The short AGI corresponded to less than 25^{th} percentile, the intermediate AGI corresponded between the 25^{th} and 75^{th} percentiles, and the long AGI corresponded to the 75^{th} percentile or above. Phthalate metabolite concentrations were also categorized into low (<25^{th} percentile), intermediate (between the 25^{th} and 75^{th} percentile) and high (>75^{th} percentile) levels. The study found levels of nine urinary phthalate metabolites in the maternal urine. Several phthalates were found to be statistically significant in relation to anogenital distance: MBP had a p value of <0.031, MBzP had a p value of <0.097, MEP had a p value of <0.017, and MiBP had a p value of <0.007. The results showed that the mothers who had an elevated urinary prenatal phthalate score delivered male infants with a shortened anogenital distance. Nine of the ten boys who had a high quartile phthalate score corresponded to a short AGI. Likewise, ten out of eleven boys who had a low quartile phthalate score corresponded to an intermediate AGI. The remaining boys had a phthalate score in the middle quartile and showed no correlation to a large or small AGI (Swan et al., 2005).

A longitudinal cohort study performed in Finland and Denmark found a correlation between specific phthalate metabolites and lowered levels of endogenous reproductive hormones in three month old male infants. All boys were examined clinically directly after birth and again three months after birth. One hundred thirty boys were recruited in this study; 65 boys were included from each country. The samples included 29 Danish boys and 33 Finnish boys with cryptorchidism, and 36 Danish boys along with 32 Finnish boys without cryptorchidism as the control group. Mothers collected breast milk samples over a period of a couple weeks after successive feedings to assess an average exposure over a period of time. The breast milk was collected in 250 milliliter glass bottles and stored in a freezer until their three month appointment. At the appointment, blood samples were retrieved from the babies and were blindly reviewed at a laboratory in Denmark. Serum follicle stimulating hormone (FSH), luteinizing hormone (LH), and sex hormone binding globulin (SHBG) were analyzed from the blood samples using immunofluorometric assays. Serum inhibin B was analyzed by a double antibody enzyme immunometric assay. Breast milk samples were thawed and tested for phthalate monoesters, where the levels were calculated in Danish and Finnish samples and in boys with or without cryptorchidism. There were no significant differences between children with or without cryptorchidism ($p = 0.440$-0.823) or between Finland and Denmark regarding phthalate monoester concentration. Several statistically significant correlations were found between phthalate concentrations and endogenous hormone levels. Leydig cells are found in the testicles and are responsible for producing testosterone (Huether & McCance, 2008). They are involved in SHBG, LH, and testosterone levels. Increased levels of MEP ($p<0.002$) and MBP ($p<0.01$) were associated with decreased SHBG. A negative association was found between MiNP

($p<0.019$) and LH levels in the blood. Free testosterone was found to be decreased with increased levels of MBP ($p<0.033$). Sertoli cells are necessary for the development of spermatids into sperm by transporting nutrients and hormonal signals to the spermatids for maturation (Huether & McCance, 2008). They are responsible for FSH and Inhibin B levels. The study found no statistically significant relationships between phthalate exposure and Sertoli cell function (Main et al., 2006).

In another longitudinal cohort study published in 2010, 845 Danish children were examined for associations between urinary phthalate levels and thyroid function and growth, determined by the insulin-like growth factor I (IGF-I). The children had been recruited before birth and were among 1,953 women who had received prenatal care in one of three university hospitals in Copenhagen, Denmark. After delivery, the children were examined at 3, 18, and 36 months of age using standardized measurements with a Kiddimeter to the nearest tenth of a centimeter. Consent was given for 845 children who were able to give a spot urine sample. Along with the urine sample, the childrens' height and weight were recorded, along with a clinical assessment of their pubertal (Tanner) stage, ultrasound of their thyroid gland including the size, and blood samples. The parents also completed a questionnaire on health and lifestyle. Twenty six children were excluded from the sample due to heart disease (3), brain tumor (1), Langerhans cell histiocytosis (1), diabetes (2), epilepsy (3), cerebral palsy (1), chronic gestational diseases (2), juvenile arthritis (1), pathological thyroid function tests (3), or puberty (12). The peripheral venous blood samples were stored in a centrifuge at -20°C until analysis. The tests were performed blindly and in random order. Thyroid tests (TSH, T4, free T4, T3, and free T3) were measured using an electrochemiluminescence. The growth factor IGF-I was

measured using a solid-phase enzyme-labeled chemiluminescent immunometric assay. All of the urine samples were collected in polyethylene cups and stored at -20°C until analysis. The samples were tested for concentrations of twelve phthalate metabolites: "monoethyl phthalate (MEP) from diethyl phthalate (DEP); mono-*n*-butyl phthalate and monoisobutyl phthalate (MBP) from di-*n*-butyl and DBP; monobenzyl phthalate (MBzP) from butyl benzyl phthalate; mono-(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) from DEHP; mono-*n*-octyl phthalate (MOP) from di-*n*-octyl phthalate; and monoisononyl phthalate (MiNP) and monocarboxyisooctyl phthalate (MCiOP) from diisononyl phthalate (DiNP)" (Boas et al., 2010). Analyses adjusted for age and sex were performed comparing phthalate metabolites with total T3, free T3 and IGF-I. Urinary phthalate concentrations were adjusted for dilution by dividing by the creatinine concentration. After the concentration was corrected, few levels of phthalate metabolites correlated with statistically significant values of T3, free T3, and IGF-I. Although free T3 was not statistically significant in relation to phthalate levels in boys or girls, total T3 was significantly affected by MEP in girls ($p<0.026$). In boys, levels of MCiOP ($p<0.02$) and DEHP (0.003) were associated with decreased levels of IGF-I. The study also found negative correlations between height and DEHP metabolite concentrations ($p<0.05$) (Boas et al., 2010).

A nested case-control study was performed in Sweden on 198 children with symptomatic allergic conditions and 202 healthy children between 3-8 years of age. Medical doctors examined all 400 children during the same two weeks that their homes were professionally investigated for indoor air quality, dust sampling, and mold and water damage. Samples of dust were collected

from 390 homes, and 346 samples continued for testing after filtering further exclusion criteria. The samples were cleaned in 30 milliliter glass vials for 30 minutes using 2 milliliters of dichloromethane. The dust concentrations of six phthalates were measured: DEP, DIBP, DnBP, BBzP, DEHP, and DiNP. The geometric mean of several phthalate metabolites showed statistically significant relationships with asthma, rhinitis, and eczema in homes of the symptomatic children. Benzyl butyl phthalate (BBzP) was associated with asthma ($p<0.005$), rhinitis ($p<0.001$), and eczema ($p<0.001$). Di(2-ethyl-hexyl) phthalate (DEHP) showed a statistically significant relationship in children with asthma ($p<0.022$) (Bornehag et al., 2004).

A cross-sectional questionnaire in Bulgaria was performed to recruit children for an investigation of the role of housing conditions regarding allergies and asthma in children. The subjects had to have at least one of the three symptoms of an allergy while in the home (wheezing, rhinitis, eczema) and the control children had to deny these conditions. The inclusion and exclusion criteria selected 272 children, of which 136 were symptomatic and 136 were not. Due to refused home investigations, refused dust sampling, or inadvertent mislabeling, the sample for analysis consisted of 177 homes of 184 children. The dust samples were obtained in the child's room where the specimens were wrapped in aluminum foil and stored in freezing temperatures until analysis. In general, there were no differences between the concentration of phthalates in the dust with the case or control groups. However, a higher concentration of DEHP was found in the homes of the symptomatic children than was found in the control group ($p<0.01$ in the crude analysis and $p<0.023$ after adjusting the dilution). Similarly, children whose parents reported wheezing within the last twelve months had a significantly higher concentration of DEHP than the control group (Kolarik, Naydenov, Larsson, Bornehag, & Sundell, 2008).

Sensitizers

Two randomized national telephone surveys examined the percentage of Americans that report to be irritated by chemical fragrances. The first survey occurred in 2002-2003 and surveyed 1,057 Americans. 31.1% of the general population, 37.2% of asthmatics, and 74.4% of the chemically sensitive found scented products on other people irritating. 17.5% of the general population, 29.7% of asthmatics, and 55.6% of the chemically sensitive reported adverse health problems from air fresheners or deodorizers. The second survey was conducted in 2005-2006 and surveyed 1,058 Americans. 29.9% of the general population, 37.9% of asthmatics, and 60.2% of the chemically sensitive reported scented products on other people irritating. 20.5% of the general population, 37.2% of asthmatics, and 60.2% of the chemically sensitive reported adverse health effects from air fresheners or deodorizers. The second survey also asked about irritation from scented laundry detergents, fabric softeners, or dryer sheets, where 10.9% of the general population, 21.2% of asthmatics, and 39.8% of the chemically sensitive reported irritation. Both of the surveys showed consistency in percentages, and an increased percentage among people with asthma or chemical sensitivity (Caress & Steinemann, 2009).

In the study performed by the Environmental Working Group and Campaign for Safe Cosmetics, 24 sensitizing chemicals were found on the label of 17 name brand fragrances (Sarantis, Naidenko, Gray, & Houlihan, 2010). Eight of those sensitizers were listed by the European Nations as the "most frequently reported contact allergens", including amyl cinnamal, benzyl alcohol, benzyl salicylate, cinnamyl alcohol, coumarin, eugenol, geraniol, and isoeugenol. Six more sensitizers were listed as the "less frequently reported contact allergens", including benzyl benzoate, benzyl cinnamate, farnesol, hexylcinnamal, lilial, limonene, and linalool

(SCCNFP, 1999). Among the 38 chemicals not listed on the label, benzyl salicylate, eugenol, lilial, and limonene were listed as well known contact allergens by the European Nations but were found "generally recommended as safe" (GRAS) by the United States (Sarantis, Naidenko, Gray, & Houlihan, 2010).

In 2006, an analysis of 300 fragranced products available on the shelves of retail stores in the United Kingdom was performed to identify the chemicals used in fragranced products. The top six most frequently labeled sensitizers were linalool (63%), limolene (63%), citronellol (48%), geraniol (42%), lilial (42%), and hexyl cinnamal (42%). Linalool was the most frequently found fragrance in personal care products such as soaps, shampoos, and shower gels, found in 70 products. Linalool and limonene were most commonly found in perfumes and aftershaves, found in 103 products. Limonene was found predominately in household cleaners like detergents, found in 57 products (Buckley, 2007).

Discussion

Increased levels of maternal phthalate concentrations are associated with decreased scores in orientation and alertness in female neonates. Long term follow-up of the previous study found increased levels of low molecular weight phthalates (LMWP) consistent with increased aggression, conduct problems, and hyperactivity, especially in male children. The study also found increased attention deficits, depression, and decreased social and adaptive skills associated with LMWP levels. Another study found higher levels of MBP negatively associated with verbal IQ scores, specifically vocabulary. This tells us that, although the mechanism is unknown, phthalates interact with chemicals in the brain and are associated with an effect on children's personalities.

Preterm birth was found to be increased in mothers who had a higher MEHP level in Italy, and was also increased with levels of MBP in Mexico City. Another study showed that DBP, MBP, and MEHP are all associated with low birth weight in infants. The same study showed that increased phthalate concentrations were present in maternal blood, cord blood, and neonatal meconium of low birth weight infants. Male infants who had a high level of MBP and MiBP showed a statistically significant correlation with decreased anogenital distance. These studies all suggest that phthalates are associated with a negative effect on fetal development.

In the study performed in Denmark, growth rate and anthropometric measurements (height, weight, and BSA) showed overall negative associations with urinary concentrations of phthalate metabolites. Specifically, total T3 was decreased with high levels of MEP in girls, and IGF-I was decreased with MCiOP and DEHP in boys. Another study showed that MEP and MBP correlated with a decreased sex hormone binding globulin, MiNP correlated with a decrease in

luteinizing hormone, and MBP had a negative effect on free testosterone in male babies. All of these studies suggest that, as endocrine disruptors, phthalates are associated with negative effects on the endocrine system and the hormones associated with it.

Phthalates have also been shown to be associated with allergic reactions. BBzP was shown to cause asthma, rhinitis, and eczema in children. DEHP has been associated with asthma, and was found in increased amounts in rooms of symptomatic children. We know that fragrances can commonly cause contact allergies, and these studies have associated phthalates, along with sensitizers, as causes for childhood allergies.

Because the fragrance manufacturers do not list all of the ingredients on the label, it is difficult for the public to know which chemicals are being absorbed and/or inhaled into our bodies. There are very few published studies that have sent the fragranced products to independent laboratories to reveal the chemicals missing from the label. Not only is this costly, it is also unrealistic to independently test all fragranced products manufactured globally.

The International Fragrance Association issues chemical concentration limits that their members must comply with. The limits are established based on the assumption that adults are exposed to one sensitizer at a time. In the study performed by the Environmental Working Group and Campaign for Safe Cosmetics, 24 sensitizing chemicals were found on the label of 17 name brand fragrances. The average product tested in this study contained 10 sensitizers. The prevalence of fragrance allergies suggests that either the concentration limits are not being followed or the limit does not take into consideration interactions with other chemicals (Sarantis, Naidenko, Gray, & Houlihan, 2010).

The seventh amendment of the EU Cosmetics Directive legislated that fragranced products had to be labeled more specifically. The European Parliament suggested a "safe" level of <10 parts per million in leave-on products and <100 parts per million in rinse-off products. The levels were suggested by the European Parliament due to the unknown level at which adverse effects occur. Since the "safe" levels of most chemicals in fragrances are unknown, Europe has required more regulation of the cosmetic industry so that the consumer can avoid specific fragrance allergens irritating to the individual (Buckley, 2007).

Limitations

There is a huge lack of disclosure in the self-regulated fragrance industry. Likewise, there are a limited number of studies that examine fragranced products to assess what ingredients are classified as part of the "fragrance". The ingredients that are listed on the label, however, have minimal to no scientific knowledge available to the public. Phthalates are one of the most well studied classes of chemicals used in fragrances, but many of the scientific studies linking phthalate exposure to health issues have been performed only once in human studies and with a small sample size. Repeated tests with larger sample sizes are needed to verify the tests' accuracy. Many other chemicals in fragrances, such as synthetic musks and sensitizers, have little to no knowledge about the effects of these chemicals on human health and development. Many of the chemicals have no toxicity studies published in scientific literature but are being manufactured daily by the cosmetic industry.

The Mount Sinai studies were the first studies to report an association between prenatal phthalate exposure and neurological effects in humans. The follow-up study examining 188 children is the first study to link high levels of maternal phthalate metabolites with behavioral problems such as aggression, Attention Deficit Hyperactivity Disorder, and conduct problems. The BRIEF and BASC functioning scales are both subjective measurements. In fact, twelve surveys were excluded from the original sample due to a high Infrequency Index on the BASC-two surveys were dismissed because of a language barrier, seven surveys were excluded due to random responding, and three more surveys were released due to a negative or unrealistic evaluation of the child's behavior. Therefore, the results from this study are potentially underreported and could have stronger results than those reported.

The Korean study regarding phthalate exposure and children's IQ was also the first study performed to examine this relationship. At least sixteen metabolites in urine can be measured, yet this study only measured three based on likely exposure and technical experience. Testing for all of the phthalates would have made a stronger study. Phthalates have a short half life and are rapidly metabolized and excreted. A single urine sample was used to measure phthalate levels in the children but it may not have the same implications as measuring urine over a period of time to test chronic exposure. Further research is needed in this area to verify these associations.

In the study performed in Mexico City linking phthalate exposure with preterm birth, a small sample size of thirty preterm deliveries with thirty full term deliveries was used. Because early ultrasound is not used routinely at the IMSS clinics, gestational age was estimated by maternal recall of the first day of her last menstrual period. A stronger study needs to be replicated with a larger sample size and a more objective measurement of the fetus' age.

The study associating prenatal phthalate exposure with a decreased anogenital distance in male babies was one of the first studies performed on humans. In animals, the anogenital distance is a sensitive measure of reproductive growth and development and has been extensively shown to be associated with antiandrogen properties. The reliability of anogenital distance in humans has not been sufficiently studied, and follow-up studies into adulthood will be required to determine whether long-term effects are seen in humans after prenatal phthalate exposure. The maternal urine was collected in the third trimester, therefore the phthalate metabolite levels may not accurately reflect the exposure during the most sensitive developmental window.

The study showing an association between phthalate exposure and reproductive hormones in boys was the first study to examine that hypothesis in humans. The mothers were encouraged to collect hind milk by hand after feedings over several weeks. They were encouraged to do this by hand as to not potentially contaminate the samples with phthalates found in soft plastics, such as breast pumps. For 57 Danish mothers, information about how the milk was collected was obtained, and 26 of the mothers (46%) said they used a breast pump to collect the milk. The study did not release information regarding breast milk collection in the Finnish women. Therefore, there is a potential possibility that the milk in this study was contaminated by the plasticizers in the breast pump.

The prevalence of fragrance sensitivity was formed from a subjective telephone survey. The questions were closed-ended and used heavy words with opposite connotations, such as "irritating or appealing", and did not give a neutral option. The survey relied on self-reported information and did not investigate factors such as exposure routes or specific chemical formulations.

Nursing Implications

An important aspect of nursing is advocating for the patient. Due to scientific studies associating phthalates with child health and development issues, maternal education about these chemicals needs to begin in obstetric offices and should be included in the postpartum and pediatric units as well. Patient education about the known and potential harms of fragranced products should be extended to the community through educational inservices or interviews with local radio or television stations. There is a lack of high quality studies that examine the relationship between other chemicals and sensitizers used in fragranced products and child health, and adults need to be informed of this lack of knowledge. Providing adults with knowledge makes them able to make informed decisions about using fragranced products while pregnant and around children.

Advocating for the patient may also include advocating for public policy changes that benefit the health of patients. The European Nation has banned several phthalates from being marketed in cosmetics, and the United States needs to follow in their tracks based on the evidence about the known harms of phthalates. Currently, consumers do not have sufficient data on these chemicals that are being used around vulnerable populations. Before products are manufactured, there must be sufficient data about the safety of the products. All chemicals should be adequately tested before marketing, including effects on vulnerable populations, such as infants and children. Likewise, the Fair Packaging and Labeling Act should be amended to require that all ingredients, regardless if included in the fragrance, must be listed on the label. Consumers have the right to know which chemicals they are being exposed to. Consumers also

have the right to expect the government to protect its citizens, especially vulnerable populations, from hazardous chemicals.

Summary

Fragrance manufacturers are a multi-billion dollar industry that self-regulate the chemical ingredients in fragranced products. Currently, the Fair Packaging and Labeling Act allows cosmetic manufacturers to include potentially harmful chemicals in their formulas without listing them on the label. Phthalates are known endocrine disruptors and have been linked with decreased anogenital distance in male babies, preterm birth, and decreased behavior and executive functioning in children. Along with phthalates, fragranced chemicals can include sensitizers, which are responsible for causing allergic reactions. The European Nations have banned or restricted over 1,000 chemicals from cosmetics, while the United States has only banned or restricted 11 chemicals from use in cosmetics. This integrated research review has shown that there is a huge gap in our knowledge about the chemicals children are being exposed to. Other than phthalates, the scientific community has reported very little and the public knows even less about these chemicals. The cosmetic industry should be enforced to thoroughly test for safety in all populations before marketing.

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