**Title: Report on Public Health Concerns - Phthalates and Bisphenol A**

**To: Public Health Subcommittee, Health and Government Operations Committee of the Maryland General Assembly**

## Plain Language Summary

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Laboratory studies have demonstrated that phthalate compounds and bisphenol A - chemicals that are used in the manufacture of plastics - can mimic, or otherwise interfere with human hormones and thus create the potential for problems with normal growth and development and health.

The body naturally makes hormones, which are chemical messengers that are involved in practically every aspect of normal bodily function from maintaining blood pressure to sexual development and function. They determine growth, development, immune system function, metabolism, and reproduction. The precise function of the hormones depends on the specific hormone, and the timing and amount of the secretion reaching the receiving organ. For example during adolescence, estrogen production in women is increased, promoting the development of breast tissue. During fetal development, testosterone is responsible for the formation of the penis and scrotum in males. Hormones are even responsible for the quick production of breast milk when a mother hears her new infant cry. They are very, very powerful chemicals and it only takes miniscule amounts to elicit responses in the body. Subtle changes in hormonal systems can have profound effects, resulting in serious disease and illness.

Some man-made chemicals mimic the hormones naturally made by the body or disrupt normal hormonal actions. When man-made, hormone-mimicking chemicals are in our environment, they have the potential to disrupt our normal hormone functioning. Phthalates and bisphenol A, both of which are chemicals that are commonly found in plastic products, are known to be hormone disruptors. Recent scientific studies have connected exposure to these chemicals with altered hormone levels, reproductive effects, and increased incidence of chronic diseases.

This report summarizes what is currently known about human exposure to phthalates and bisphenol A and associated health effects.

## What are Phthalates and Bisphenol A?

**Phthalates** are a class of chemicals that are used in many household and personal care products, toys, medical supplies and in plastics. Their particular function is to improve the flexibility of the chemical product – to allow it to be more malleable. There are many different types of phthalates, which all share a basic chemical structure. Some phthalate compounds are more toxic than others. The phthalate chemicals that have been most closely associated with adverse developmental and reproductive health effects are diethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), and butyl benzyl phthalate (BBP).

**Bisphenol A** is an industrial chemical used in the manufacture of polycarbonate plastic and epoxy resins. Bisphenol A is used in a variety of consumer products including water bottles, the inside lining of cans, in some types of baby bottles, an in some dental fillings. BPA is a main ingredient in plastics and resins – it is not an "additive" like phthalates.

**Are we exposed to these chemicals – do they get into our bodies?**

Phthalates are ubiquitous in our environment. According to the U.S. Center for Disease Control's (CDC) most recent chemical exposure report, which assessed human body burdens of chemicals, phthalates were found in nearly 100% of the population. This means that EVERY one of us has man-made phthalates residing in our bodies. They are also in women's breast milk and can be passed on during breastfeeding. Levels of some phthalates in some women of childbearing age, including DBP and DEHP, exceeded the government's "safe" levels set to protect against birth defects. A report documenting levels of several phthalates in children living in the Imperial Valley, California, found these chemicals in all children examined, and the average phthalate levels found were higher than what had been reported for adults in the CDC study.

The CDC study confirmed widespread contamination of phthalates with the highest levels of DEHP, BBP, and DBP exposure in children and women of reproductive age, which raises specific concerns for potential adverse developmental effects on the fetus and children. Children's exposures begin at conception, as chemicals, including phthalates, can cross the placenta resulting in chemical exposures to the fetus during critical periods of development.

Although there are fewer studies available on exposure to bisphenol A, a study by the CDC found that 95% of Americans have detectable levels of bisphenol-A in their bodies. In this study, the observed BPA levels were at and above the concentrations known to cause adverse effects in experiments with laboratory animals.

**What harmful effects could occur as a result of exposure to phthalates and bisphenol A?**

Our understanding of the potential adverse health effects of **phthalates (DEHP, DBP, and BBP)** comes from both laboratory animal and human epidemiological studies. Observations made in laboratory animal studies that are also seen in human studies, increase our confidence in forming associations between exposures and health effects. In particular, several recent animal and human studies on a variety of phthalates have raised concerns that exposure may be associated with the following health outcomes:

- Genital defects including cryptorchidism (undescended testicles) and hypospadias (the urethral opening is located along the shaft of the penis, rather than at the tip)
- Decreased testosterone production in boys
- Decreases in male fertility, impaired semen quality, and sperm damage in men

Numerous laboratory animal studies, as well as a handful of human observational studies, have identified a variety of reproductive, developmental, and metabolic effects stemming from environmentally-relevant low-level exposures to **bisphenol A (BPA).** Some of the principle adverse health effects that have been associated with exposure to bisphenol A include:

- Alterations in brain development, specifically, in laboratory animals altered sexual differentiation, accelerated puberty, and altered reproductive cycle
- Reduced sperm count in laboratory animals
- Prostate disease and cancer in laboratory animals
- Breast cancer in rodents
- Diabetes and obesity in mice
- Behavioral changes (Including hyperactivity in rats, increase in aggression in mice, changes in response to painful or fear-provoking stimuli, reversal of normal sex differences in the brain structure and elimination of sex differences in behavior, decreased maternal behavior, altered play and other socio-sexual behaviors, and increased susceptibility to drug addiction.)

Not all studies of BPA yield the same results; several large laboratory animal studies did not indicate low dose effects from BPA. In a very persuasive review of 151 studies on the low-dose effects of BPA, note that none of the 12 studies **funded by the chemical industry** reported adverse effects at low levels, whereas **128 of 139 government-funded studies found effects**. One industry study concluded BPA caused no effect, but an independent analysis of the data by scientists convened by the National Toxicology Program of the U.S. Department of Health & Human Services concluded and that there was an effect. In fact, recent studies of bisphenol A, focusing on reproductive and developmental endpoints, have identified adverse effects at exposure doses that are lower than what is considered to be a safe dose both in the United States and in Europe.

**Are the exposures likely to result in harm?**

Studies on exposure to phthalates and bisphenol A have detected these chemicals in nearly every person tested. These chemicals are commonly found in numerous consumer items that we are in contact with every day. We know that these chemicals are associated with a variety of hormone disruptive actions based on many different animal and human studies, and there is evidence to suggest that the exposure concentrations could reach levels of concern - particularly for vulnerable populations.

**Report on Public Health Concerns - Phthalates and Bisphenol A**
**Technical Review**

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## Introduction to Hormones and Endocrine Disruption Studies

Hormones are important chemical communication molecules: secreted directly into the blood, hormones move through the circulatory system to convey signals that elicit a response in the target tissue. The precise function of the hormones depends on the specific chemical, and the timing and amount of the secretion reaching the receiving organ. For example during adolescence, estrogen production in women is increased, promoting the development of breast tissue. During fetal development, testosterone is responsible for the formation of the penis and scrotum in males. Hormones are part of a complex system of physiological regulation; they determine growth, development, immune system function, metabolism, and reproduction. Subtle changes in hormonal systems can have profound effects, resulting in serious disease and illness. Conditions that affect the production of thyroid hormones can lead to hyper- or hypothyroidism, while conditions that affect the release of pituitary gland hormones can depress ovulation leading to infertility.

It is important to understand that the use of laboratory animals, such as mice and rats, in the study of complex hormone effects is essential, because it allows researchers to control exposures during multiple generations. It also permits the detailed analysis of the effects of chemicals on organs and tissues to determine the sequences of events that occur leading up to visible adverse effects. This type of research simply cannot be done on humans. Therefore, by using laboratory animals we are able to develop hypotheses that can be carefully tested by measuring chemical exposures in humans, and observing adverse outcomes.

Laboratory studies using rats and mice have demonstrated that certain chemicals, phthalates and bisphenol A, found in some plastic toys, and in everyday household and personal care products, can interfere with hormone function (endocrine disruption). The mechanisms by which chemicals interfere with hormone function vary by chemical and by the target in the body. Some chemicals can act as hormone mimics, while others can block hormone action. Some chemicals alter the availability of the hormone at the specific tissue location. Low doses can be more potent modulators of hormone systems than high doses. This raises several important questions:

1. Are we exposed to these chemicals – do they get into our bodies?
2. What harmful effects could occur?
3. Are the exposure concentrations likely to result in harm?

It can be very difficult to define cause and effect in hormone systems because the specific effects of endocrine disruptors may affect different endpoints at different ages, meaning that there are different windows of vulnerability [1]. We also face the challenge of trying to understand the potential adverse effects of individual chemicals, knowing that we are exposed to a range of different chemicals throughout our lifetime. It is extremely difficult to study the effects of multiple chemical exposures since the potential chemical combinations are nearly infinite.

Therefore, we must use a combination of laboratory animal studies and human outcome studies to assess the effects of chemicals on human health.

**A few important (and unavoidable) terms and phrases:**

**Cryptorchidism:** This birth defect is characterized by the absence of testis in the scrotum, usually as a result of the failure of the testis to "descend," during fetal development. About 1 in 500 men born with one or both testes undescended develops testicular cancer, roughly a 4- to 40-fold increased risk. Three – 5% of full-term infant boys are born with at least one undescended testis, making cryptorchidism the most common birth defect of male genitalia [2].

**Dose:** The amount of a substance that actually gets into the body, as opposed to the exposure concentration which is measured in a medium outside of the body. Dose can be presented per unit body weight or as simple mass For example, if a 100 kg person ingests 10 mg/kg of a substance per day, then the individual would ingest a total of 10 x 100 = 1000 mg per day. This is different than the exposure concentration, which represents the amount of chemical found in air, water, food, etc.

**Endocrine disrupting chemicals:** The endocrine system is a term used to describe collectively the systems that rely on hormones for chemical communication. Endocrine disrupting chemicals are chemicals that can alter the function of hormones.

**Epidemiological study**: The study of factors influencing health and illness in humans. Within the context of this paper, epidemiological studies involve the measurement of exposure to chemicals (e.g., concentrations of chemicals in blood or urine), and adverse health effects, and then performing a statistical analysis to see if exposures are associated with the adverse health effects.

**Exposure versus Dose:** The term exposure generally refers to the concentration of a chemical in the environment – air, water, food, etc. The term dose is used in a very specific sense: amount of the chemical per unit of body weight per day. Units of measurement of dose are generally milligram per kilogram of body weight per day, or mg/kg/day. Sometimes, micrograms (µg) are used in place of milligrams; there are a thousand micrograms in a milligram. Therefore 0.010 mg/kg = 10 µg/kg.

**From Genes to Proteins:** Proteins are made from amino acids, and are critical components of cells and tissues. The selection of amino acids is determined by the sequence of nucleotides in DNA. DNA is first transcribed by RNA, which is then translated into the proteins. Chemicals can interfere with this process in many different ways; they can modify the DNA itself, they can block or enhance the transcription of DNA into RNA; they can alter the translation into proteins.

**Hormones:** Hormones are chemical messengers that are released by one cell type and act on another cell type. Most hormones signal cells to make a change by combining with a receptor. Hormone effects include stimulating or inhibiting growth, activation or suppression of the immune system, and the regulation of metabolism. It is not unusual for hormones to have multiple effects on cells from different organ systems, and different effects at different times in a

person's life. For example estrogen not only regulates responses in the female reproductive system (e.g., breast development, reproduction, menopause), but also regulates the development of the brain in the fetus, newborn baby, and adolescent.

**Hypospadias:** This is a birth defect of the urethra in the male that involves an abnormally placed urethral opening. Rather than opening at the tip of the glans of the penis, the urethra opens anywhere along the underside of the shaft of the penis. Hypospadias are the second most common birth defect of male genitalia. Occurrence rates have been estimated at 1 in 125 males [3].

**Metabolism and Metabolite:** When we are exposed to chemicals, our body may metabolize, or breakdown the chemicals, which helps to eliminate them from our body. The breakdown product is called the metabolite. For each chemical that enters the body there may be several different metabolites. Sometimes, the metabolite is more toxic (harmful, or biologically active) than the parent compound.

**Reference Dose:** An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral dose to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

## PHTHALATES AND BISPHENOL A: HEALTH EFFECTS

### Background

Laboratory studies have demonstrated that certain phthalate compounds, and bisphenol A - chemicals that are used in the manufacture of plastics - can mimic human hormones. Known collectively as endocrine disrupting compounds, these chemicals are ubiquitous in our environment, and can be found in 95% of humans. Recent studies have focused on determining if there is an association between human exposures to phthalates and bisphenol A, and adverse health effects, such as altered hormone levels, reproductive effects, or increased incidence of diseases, including cancer. The following report summarizes what we currently know about human exposure to these chemicals, and associated health effects.

### SYNOPSIS OF SCIENTIFIC RESEARCH

***What are Phthalates?***

Phthalates are a class of chemicals that are used in many household products and personal care products, and in plastics to improve flexibility. There are many different types of phthalates, which share a basic chemical structure. As described below, some phthalate compounds are more toxic than others. The phthalate chemicals that have been most closely associated with adverse developmental and reproductive health effects are diethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), and butyl benzyl phthalate (BBP).

Many plastic toys are made from polyvinylchloride (PVC) plastics. PVC is a brittle plastic and is commonly used to make pipes used in household plumbing. Soft, flexible plastics that are used to make toys or that are used in medical supplies often include a plasticizing or softening

agent, such as phthalates. But phthalates are not bound to the PVC, and therefore over time sloughs off. Certain conditions increase the release of phthalates from the plastics: contact with fats, oils, saliva, and temperatures over 85° F.

***What is Bisphenol A?***

Originally produced for use as a synthetic hormone in 1936, bisphenol-A (BPA) is currently used in the production of some polycarbonate plastics, including baby bottles and water bottles, epoxy resins that are used to coat the inside of cans, and in white dental sealants. It may also be found in certain plastics used in children's toys. Bisphenol A is now one of the most commonly used chemicals in industrial manufacturing. In contrast to phthalates, bisphenol A is bound within the polycarbonate plastic, however the chemical bond is unstable, and degrades under a variety of mild conditions, such as increased temperature, contact with saliva, etc.

***We are all Exposed…***

Government studies have shown that nearly all residents in the United States are exposed to numerous phthalates, and to bisphenol A.

*Phthalates*

The U.S. Centers for Disease Control (CDC) released its initial report on phthalate exposures in 289 adult Americans tested [4]. The results of this CDC study indicate that all individuals were exposed to phthalates, and that levels of some phthalates in women of childbearing age, including DBP and DEHP, exceeded the government's "safe" levels set to protect against birth defects [5]. These results were surprising but additional studies only confirmed the results of the initial CDC study. For instance, a report documenting levels of several phthalates in children living in the Imperial Valley, California, found these chemicals in all children examined, and the average phthalate levels found were higher than what had been reported for adults in the CDC study [6].

The CDC confirmed widespread contamination of phthalates with the highest levels of DEHP, BBP, and DBP exposure in children and women of reproductive age, which raises specific concerns for potential adverse developmental effects on the fetus and children [7, 8]. According to the CDC's most recent chemical exposure report, which was issued in 2005, phthalates are found in nearly 100% of the population [9]. The CDC survey found that of the 12 phthalates tested by the CDC, eleven were concentrated more highly in children than in adults, and higher in females than males.

*Bisphenol A*

There are fewer studies available on exposure to bisphenol A, although bisphenol A will be included in the next round of sampling by the U.S. Centers for Disease Control and Prevention (CDC), as part of their national biomonitoring effort. According to the CDC, 95% of Americans have detectable levels of bisphenol-A in their bodies [10]. In this study, the observed BPA levels detected—0.1 to 9 parts per billion (ppb) were at and above the concentrations known to reliably cause adverse effects in experiments with laboratory animals.

***How are we exposed?***

**Phthalates**

As noted previously, there are many different types of phthalates, which share a basic chemical structure. It is generally assumed that the most important exposure route is ingestion, however there are some studies that suggest that inhalation can also be an important exposure route [11, 12, 13, 14, 15, 16]. A study by Adibi and colleagues (2003) identified a correlation between concentrations of phthalates in indoor air within the home and urinary excretion of phthalate metabolites. For personal care products, such as lotions, dermal (skin) exposure is clearly relevant, and a recent CDC study demonstrated that phthalate exposure correlates with the use of multiple phthalate-containing personal care products, such as hair gel, deodorant, and cologne [17], although it is likely that these exposures represent some combination of inhalation and dermal exposure.

**Bisphenol A**

Bisphenol A is used in polycarbonate plastics, and numerous studies have documented that BPA can leach or migrate from the polycarbonate plastic into food and beverages during common use activities [18, 19, 20, 21]. In one study, BPA leaching was detected in polycarbonate baby bottles after dishwashing, brushing, and boiling. Levels of BPA detected in liquid held in 12 polycarbonate baby bottles exceeded 8 µg/L after 51 washing cycles [22]. Certain brands of dental sealants, commonly applied by dentists to protect teeth, contain BPA, and may be a source of exposure to BPA at concentrations that show health effects in rodents [23]. The study authors emphasize that while dental sealants should continue to be used, the brands that are not associated with BPA exposure should be favored.

**Pregnant women and Children are at Greatest Risk**

Children are considered to be particularly vulnerable to the effects of chemicals in their environment because they face greater exposures due to their size and behaviors, and because they are more sensitive as a result of their ongoing development [24, 25]. Infants and young children have structural and functional characteristics that while common to their normal growth and development may actually increase their vulnerability to chemicals. These characteristics include a larger body surface area in relation to their weight, a higher metabolic rate and oxygen consumption and therefore a greater intake of air per unit body weight [26]. In general, infants absorb chemicals more readily than adults and the immaturity of the infants' liver and kidneys result in reduced capacity for detoxification and excretion. Given the same dose of a chemical, the infant will tend to accumulate a greater percentage of that dose [26]. In addition, infants and young children may increase their exposures to toxicants in the environment by their hand-to-mouth behavior, which encourages them to place objects such as toys into their mouth.

Children's exposures begin at conception, as chemicals, including phthalates [27,28,29] and BPA [30], can cross the placenta resulting in chemical exposures to the fetus during critical windows of development. Therefore we have special concerns regarding the chemical exposures in women of childbearing age. Children have not yet developed the protective biochemical mechanisms to minimize or repair damage following exposures to chemicals. (Consider, for example, how some medications should not be given to children, or are prescribed at a much lower dose). Importantly, children's brains and other organ systems are constantly developing, and there are certain windows of particular sensitivity to damage or disruption. For these

reasons, caution is urged in protecting children from exposures to chemicals that may impact them later in life.

**Web-based Resources on Phthalates and Bisphenol A**

Environment California (Information and action on chemicals in toys)
http://www.environmentcalifornia.org/environmental-health/stop-toxic-toys

Not Too Pretty (A report on phthalates and bisphenol A, among other chemicals, in cosmetics)
http://www.nottoopretty.org/

Our Stolen Future (Information on phthalates)
http://www.ourstolenfuture.org/NEWSCIENCE/oncompounds/phthalates/phthalates.htm

Our Stolen Future (Information on bisphenol A)
http://www.ourstolenfuture.org/NewScience/oncompounds/bisphenola/bpauses.htm

## What are the Health Effects of Concern for Phthalates?

Our understanding of the potential adverse health effects of phthalates comes from both laboratory animal and human epidemiological studies. Although there is no such thing as "proof" in science (rather hypotheses are confirmed and refined, in an incremental process of investigation), observations made in laboratory animal studies that are also seen in human studies, tend to increase our confidence in our hypotheses. Several recent examples have raised concerns among public health officials. For example, when pregnant rats are given phthalates during a critical window of development the male offspring exhibit "phthalate syndrome", characterized by malformations of the internal and external sex organs [31]. Medical researchers have identified subtle developmental effects, similar to those seen in animal studies, in male babies exposed to phthalates during pregnancy [32]. Some researchers suggest that exposure to phthalates, along with the observed subtle developmental changes, may be associated with decreases in male fertility [33].

Additional concerns regarding the potential adverse effects of phthalates include the potential exacerbation of asthma or lung ailments for children breathing dust contaminated with phthalates [34], and even skin allergies [35]. Several high profile reports have evaluated the relationship between exposure to phthalates and a variety of immune system responses, and this is described in more details, below.

**This review of health effects associated with exposure to phthalates begins with a brief description of the main phthalate chemicals of concern. This is followed by a description of the adverse health effects identified in both laboratory animal and human epidemiological studies.**

### *Introduction to the Phthalate Chemicals of Concern*

The three phthalates that are most closely associated with developmental and reproductive toxicity are diethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), and benzylbutyl phthalate (BBP). The sources and nature of exposures to these chemicals are described below. The majority of the information described below has come from the following websites:

Agency for Toxic Substances and Disease Registry (ATSDR): Toxicological Profiles.
http://www.atsdr.cdc.gov/toxpro2.html#d

Agency for Toxic Substances and Disease Registry (ATSDR): ToxFAQs.
http://www.atsdr.cdc.gov/toxfaq.html

National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction:
http://cerhr.niehs.nih.gov/

DEHP:
DEHP is the primary phthalate used to make polyvinyl chloride (PVC) plastic soft and flexible. DEHP is found in a variety of plastics used in health care, including, enteral feeding sets, nasogastric tubes, blood bags and filters, and IV bags and tubing. DEHP is also found in plastic clothing (such as raincoats), vinyl floor tiles, soft vinyl toys, and vinyl tablecloths. Exposure to DEHP can occur through air, water, or skin contact with plastics that have DEHP in them. Food may also contain DEHP, but contamination levels vary considerably and estimates are uncertain.

BBP: BBP is an industrial solvent used in vinyl floor products, adhesives, sealants, cosmetics, and car-care products. In a recent CDC study, mono-benzyl phthalate, which is created in the body from benzylbutyl phthalate, was present in the urine of children aged 6-11 at a concentration more than three times higher than that found in people aged 20 and older [36].

DBP: DBP can be found in fragrances, colognes, hairspray, nail polish, and other personal care products. It can also be found in carpet backings, paints, glue, insect repellents, and rocket fuel. DBP is also an ingredient in some types of enteric coatings used in some medications [37]. Exposure to low levels of di-n-butyl phthalate in the air is extremely common because it is used in so many household products. Use of personal care products containing DBP could result in exposure through the air (breathing) or skin absorption. Foods that are packaged or stored in materials containing DBP could also be a source of exposure.

***Some of the potential adverse health effects of phthalates include:***

**Genital defects and reduced testosterone production in boys:** In an important human epidemiological study, Dr. Shanna Swan and her colleagues found a strong relationship between exposure of mothers to phthalates during pregnancy and changes in the size and anatomy of the genitalia of their male babies and toddlers. Mothers with the highest levels of phthalate metabolites, including DBP, and BBP metabolites, in their urine late in their pregnancies had babies with a shorter anogenital distance (the space between the anus and penis that forms into the scrotum in males), smaller penises, and more instances of incompletely descended testicles [38]. These effects were seen at phthalate levels below those found in one-quarter of women in the U.S., based on CDC data. The pattern of genital changes seen in these baby boys is consistent with the "phthalate syndrome" (i.e., increased frequency of undescended testicles and genital deformations and impaired sperm quality) observed in rodents prenatally exposed to phthalates and suggestive of "testicular dysgenesis syndrome," a human health condition with the same characteristics and linked to phthalate exposure. An important component of this syndrome is an increased risk of testicular cancer.

Another recent study looking at the impact of phthalate exposure on over 100 three-month-old baby boys in Denmark and Finland showed reduced testosterone production and other endocrine abnormalities [39]. The data on reproductive hormone profiles and phthalate exposures in newborn boys provides additional evidence that human testicular development and function may be vulnerable to perinatal exposure to some phthalates, including DBP, DEHP, diethyl phthalate (DEP), and diisononyl phthalate (DINP). The findings are thus consistent with the above study showing incomplete masculinization of infant boys exposed to phthalates prenatally.

The similarities between the male reproductive defects induced by phthalates in rodents, described below, and the features of male birth defects seen in humans are strong [40]. In rodents, interference with testosterone production during fetal development has effects on a wide array of processes, primarily targeting the male genital tract.

**Genital defects, rodent studies:** As reported by Fisher et al. [41], cryptorchidism (undescended testicles) and hypospadias (the urethral opening is located along the shaft of the penis, rather than at the tip) are the two most common congenital malformations in children [42]; 6±8% of men have subnormal sperm counts; and the lifetime risk of testicular germ cell cancer is 0.3±0.8% in Caucasian men [43]. The presence of any of these disorders is considered risk factors for the others, and each disorder is associated with the abnormal development of **Sertoli and Leydig cells** (found in the testes and related to testosterone production). Therefore this collection of disorders has been named `testicular dysgenesis syndrome' (TDS) [44]. According to Fisher [40], human TDS can be mimicked in rats by the administration of the phthalate DBP. Fisher et al [41] were able to induce the development of cryptorchidism, hypospadias, infertility, and other testicular defects by administering DBP to female rats during the third week of pregnancy.

Three different phthalates, DEHP, BBP, and DINP, were found to disrupt sexual development in male rats, resulting in hypospadias, cleft phallus, reduced testes weight, and cryptorchidism [45]. Parks et al. [46] demonstrated that DEHP reduces testosterone production in the developing rat testes, thus interfering with the critical hormone signals that direct normal male reproductive development. Specifically, exposure to DEHP during pregnancy resulted in decreased testosterone levels in male offspring. In one recent study, researchers demonstrated that the phthalates DEHP, BBP, and DINP reduce the levels of insulin-like hormone #3. Decreased levels of this hormone has been associated with undescended testicles in mice [47], so this study provides some information about how phthalates may disrupt specific hormones leading to aberrant testicular development. Other research groups have implicated DBP as a direct cause of hypospadias and cryptorchidism in rodents [48, 49]. Lehmann et al. [50] demonstrate that in utero exposure to DBP alters genes that control the movement of cholesterol and the production of steroids, resulting in decreased testosterone production in the fetal testis. It is notable that the lowest doses at which adverse reproductive and developmental effects were observed are within an order of magnitude of the highest exposures measured in humans, suggesting that the margin between common human exposures and exposures with adverse effects may be too close for comfort.

**Impaired semen quality and sperm damage in men:** Several studies show as association between phthalate exposure and sperm damage and impaired semen quality in men. In three studies in particular, the phthalate levels associated with the damage were well within the range

experienced by many American men. In one study, Harvard and CDC scientists show men with higher phthalate levels are more likely to have low sperm count and impaired sperm quality [51]. The highest phthalate concentrations were found in men with the lowest sperm counts. Notably, American men often have phthalate levels two to three times higher than those associated with sperm damage found in this study. In another study by the same research group, the scientists discovered that sperm DNA damage, including reduced sperm count, lower sperm motility, and deformed sperm, is more likely in men with elevated phthalate levels—such as DBP, BBP, and DEP [52]. Finally, another study found significantly higher levels of phthalates in infertile men whose sperm was abnormal or had DNA damage [53].

**Neurological development:** Estrogen is a potent modulator of male and female fetal and neonatal brain development, particularly in the region of the brain that controls sexual development. In a laboratory study, rats exposed to DEHP at environmentally relevant concentrations (e.g., exposures that can be found in the environment) during fetal and neonatal development demonstrated alterations in the function of an enzyme (aromatase) in the brain that controls the availability of estrogen in the brain [54]. In male rats, low-level exposures were associated with the inhibition of estrogen availability, while higher exposures stimulated estrogen availability [54]. In a related study, DEHP exposure was associated with impaired testicular function and induced reproductive tract abnormalities in male offspring [55].

**Premature delivery:** Rates of premature birth have been steadily rising over the last two decades, and several studies suggest a link between phthalate exposures and premature delivery [56, 57, 58]. In one study, scientists found higher levels of the primary DEHP metabolite in the cord blood of newborn infants correlated with higher incidence of premature delivery [56].

**Endometriosis in women:** In a recent study of Indian women suffering from infertility, women with endometriosis had significantly higher blood levels of di-n-butyl phthalate (DBP), butyl benzyl phthalate (BBP), di-n-octyl phthalate (DnOP) and diethyl hexyl phthalate (DEHP), compared to women without endometriosis [59].

***How do animal doses compare to human exposures?***

The US Environmental Protection Agency's draft reference dose for dibutyl phthalate is 0.3 mg/kg per day [60]; the EPA reference dose for diethylhexyl phthalate is 0.02 mg/kg/day [61]; and the EPA reference dose for benzylbutyl phthalate is 0.2 mg/kg per day [62]. Estimated doses of some of the phthalates have recently been calculated and the average estimated daily human dose for dibutyl phthalate is approximately 0.001 mg/kg/day [63]. The 95$^{th}$ percentile of the estimated daily DBP dose is nearly 0.0027 mg/kg/day, and the highest estimated value is approximately 0.006 mg/kg/day [63]. Exposure to DEHP is higher, with estimated doses ranging from a median of 0.0013 mg/kg/day to a maximum of 0.041 mg/kg/day, whereas exposure to BBP is more variable, with estimated doses ranging from a median of 0.0005 mg/kg/day to a maximum of 0.015 mg/kg [63].

| Chemical Name | Reference Dose, mg/kg/day | Median Dose, * mg/kg/day | Maximum Dose, * mg/kg/day |
|---|---|---|---|
| Dibutyl phthalate | 0.300 | 0.001 | 0.006 |

| | | | |
|---|---|---|---|
| Diethylhexyl phthalate | 0.020 | 0.0013 | 0.041 |
| Benzylbutyl phthalate | 0.200 | 0.0005 | 0.015 |

* Estimated by Marsee et al. 2006

Note that individuals exposed to the highest levels of DEHP are exposed to this compound at a level that is above the "safe" reference dose, and individuals exposed to the highest levels of BBP are within an order of magnitude of the reference dose. It should be emphasized that all individuals are exposed to multiple phthalate compounds, and there is significant uncertainty regarding the health effects resulting from exposure to mixtures of phthalates.

**Summary: Health Concerns for Phthalates**

There is clear evidence that in utero exposure of rodents to DEHP, DBP and BBP can cause alterations in the male reproductive system. There is a growing body of evidence that is suggestive that in some individuals, phthalates may be contributing to observed birth defects in male babies. However, there are caveats: there are inconsistencies in the associations between birth defects and exposures to specific phthalates, and humans are exposed to very low levels of many different chemicals, making it difficult to link exposures to specific chemicals with adverse outcomes. This is particularly true for hormone systems, which are quite complex, have lots of redundancies and feedback loops, and specific windows of vulnerability that open and close over a lifetime. Although researchers are closing in on specific pathways that may be impaired by phthalates, there is still a lot of work to be done to better characterize exposure and outcomes in humans.

**What are the Health Effects of Concern for Bisphenol A?**

Bisphenol A (BPA) was first manufactured as an estrogen mimic. The current safe level (reference dose) of BPA exposure is 0.05 mg/kg/day (50 µg/kg/day), and was set by U.S. EPA is based on experiments conducted in the 1980s. In Europe, the safe dose is considered to be 0.010 mg/kg/day (10 µg/kg/day) [64]. Recent studies, focusing on reproductive and developmental endpoints, have identified adverse effects at exposure doses that are lower than what is considered to be a safe dose both here and in Europe. A selection of these studies is described below.

***Some of the potential adverse health effects of bisphenol A include:***

**Alterations in Brain Development:** Hormones such as estrogen and progesterone provide critical cues for brain development. Low doses of BPA can disrupt important effects of hormones in the developing brain. In most studies, BPA has been found to mimic the actions of estrogen in developing neurons, resulting in alterations in the regions of the brain associated with sexual differentiation. Specifically, in laboratory animals we see altered sexual differentiation, accelerated puberty, and altered reproductive cycles [1]. An additional concern related to this finding is that this type of disruption is associated with impaired learning and memory [65, 66].

Just as hormones are critical for normal neurological development, so are the receptors to which hormones bind to effect cellular changes. Low-dose exposure to BPA increases progesterone receptor RNA message levels at 400 µg/kg/day [67]. Aloisi et al [68] noted changes in estrogen receptor RNA levels at 40 µg/kg/day of BPA, whereas Ramos et al. [69] noted changes in estrogen receptor RNA at 25 µg/kg/day of BPA. BPA modulates the receptor of somatostatin, a hormone that inhibits the release of growth hormone, thyroid stimulating hormone, and insulin. BPA altered the expression of brain somatostatin receptors at 400 µg/kg/day of BPA [70]. In short, BPA has been shown to alter the expression of receptors that are involved in regulating the brain control systems that coordinate the functioning of the reproductive system as well as reproductive and other social behaviors.

**Reduced sperm count:** Several studies show that low-dose exposures of adult male rats, at levels between 0.2 and 20 µg/kg/day reduce daily sperm production and fertility [71, 72, 73, 74]. In the studies by Chitra et al, and Sakaue et al. male rats were administered low-doses of BPA. Rats exhibited decreased sperm count in both studies, and decreased testicular and epididymal weights, and increased prostate weights in the Chitra study. Male mice given extremely low doses of BPA also exhibited reduced sperm production [72, 74]. Altered hormone levels may be associated with changes in sperm production. Two examples of altered hormone levels in male rats are the alteration of plasma luteinizing hormone levels following low dose BPA exposure (2 µg/kg/day) in maternal rats [75], and decreased plasma testosterone in males following low dose BPA exposure (2 µg/kg/day) in maternal rats [75; 76].

**Prostate disease and cancer:** Maternal low-dose exposure to BPA was correlated with increased prostate size in mouse male offspring [77, 78, 79]. These studies show an increase in prostate size due to hyperplasia (cell overgrowth) in the male mouse offspring. Another study shows extremely low doses of BPA initiate the growth of human prostate cancer cells grown in

the laboratory [80]. In another study, the exposure of laboratory animals to BPA during fetal development was shown to increase susceptibility to prostate cancer in male rats later in life [81]. Rather than directly modifying DNA, like most known cancer-causing agents, bisphenol A alters the way that key segments of DNA are translated into proteins that control how cells function. Although BPA is thought to increase cancer risk, it does not do so in the "normal" way. This important new area of research raises questions regarding exposures during critical windows of development [82].

**Breast cancer:** Recent studies show that low-dose BPA exposure stimulates mammary gland development [83, 84], and that prenatal exposure to BPA causes long-lasting changes in female rat breast tissue that make the tissue more sensitive to estrogen at puberty and more susceptible to cancer-causing chemicals as adults [85]. Estrogen exposure is one of the main risk factors for breast cancer, and sensitivity to estrogen exposure may be an important factor in the development of breast cancer. Animals exposed in utero to BPA have a significantly higher sensitivity to estradiol (a form of estrogen) [83]. BPA also increases ductal density in laboratory animals, which is another breast cancer risk factor for humans [83].

**Diabetes and obesity:** In a recent laboratory animal study, short-term exposure to BPA at doses close to, or below the current reference dose (presumed to be safe for humans), changes blood glucose levels and causes insulin resistance in adult mice [86]. Insulin functions to transport glucose from the blood into cells, which use glucose as a source of energy. Insulin resistance, when insulin loses its ability to remove the glucose from the blood circulation, is strongly associated with the development of Type II diabetes in people, in addition to being related to other chronic health effects such as hypertension and cardiovascular disease. The exposure levels in this recent study shows that even a single dose of BPA at levels currently found in humans can result in altered levels of blood glucose and insulin, and twice-daily exposure for just four days results in insulin resistance. Additionally, BPA has been shown to alter important cell signaling processes in pancreatic cells [86], which may help explain why BPA is associated with insulin resistance.

Since diabetes is closely tied to being overweight, the effects of BPA on weight gain and fat metabolism are of interest, but for now continue to be speculative. There is a complex relationship between fat cells, blood glucose levels and insulin. Glucose can be converted to starch and stored in the liver, or it can be converted to fatty acids and stored in fat cells. Fat cells produce chemicals that can block the function of insulin resulting in insulin resistance. BPA has been shown to increase glucose uptake in the fat cells of mice, which could be related to the development of insulin resistance [87].

**Behavioral changes:** Hormones have a significant impact on neurological development. The concern is that BPA can interfere with neurological development in such a way that influences behavior. Several laboratory studies have demonstrated that low-dose exposure to BPA causes behavioral effects in laboratory animals, including hyperactivity in rats [88], increase in aggression in mice [89, 67], changes in response to painful or fear-provoking stimuli [90], reversal of normal sex differences in the brain structure and elimination of sex differences in behavior [91], decreased maternal behavior such as reductions in time spent nursing, increases

in time out of the nest and away from offspring [92], altered play and other socio-sexual behaviors [90, 93], and increased susceptibility to drug addiction [94, 95].

**Miscarriage and polycystic ovarian disease in women:** Several studies suggest an association between exposure to low doses of BPA and miscarriages in women. Scientists examined patients who had suffered three or more consecutive miscarriages and compared the blood BPA levels to women who had no previous miscarriages [96]. The results indicate that women with multiple miscarriages had three times the level of BPA in their blood than women who had never miscarried.

In another study, women who had polycystic ovary syndrome (PCOS) had higher levels of BPA, were more obese, and had higher levels of male sex hormones, including testosterone and androstenedione [97].

**Early puberty:** Low-dose exposure to BPA may influence the timing of the onset of puberty. Several studies in laboratory animals reveal the early onset of sexual maturation in females occurring at maternal doses between 2.4 and 500 µg/kg per day [98, 99, 100].

**Thyroid hormone action:** BPA provided to rats at doses ranging from 1- 50 mg/kg/day during pregnancy and lactation was associated with an increase in serum total T4 (the thyroid hormone thyroxine) in pups on postnatal day 15, although T4 concentrations appear to be equivalent to controls by postnatal day 35 [101]. In an earlier study, the ability of bisphenol A to bind thyroid hormone receptors was demonstrated [102]. Collectively, these studies suggest that mechanisms of endocrine disruption beyond altered estrogen or testosterone regulation must be considered.

**Summary: Health Concerns for Bisphenol A**

Studies evaluating the potential health impacts of exposures to bisphenol A indicate the potential for a variety of reproductive, developmental and metabolic effects. The major focus of these studies is on effects stemming from environmentally relevant low-level exposures. Not all studies yield the same results; several large laboratory animal studies did not indicate low dose effects from BPA [103]. In a very persuasive review, vom Saal demonstrates that of 151 studies on the low-dose effects of BPA, none of the 12 studies funded by the chemical industry reported adverse effects at low levels, whereas 128 of 139 government-funded studies found effects [104]. Even the 12 industry-funded studies have flaws, however. Of the industry studies, two had its positive control fail—an indication that the there was a problem with the study. Another industry study concluded BPA caused no effect, but an independent analysis of the experiment's data by scientists convened by the National Toxicology Program of the U.S. Department of Health & Human Services concluded that in fact there was an effect. Industry scientists had misreported their own results.

**A review of city, state, and international attempts to regulated Phthalates and Bisphenol A**

**California Safe Cosmetics Act of 2005** will require manufacturers to report the use of potentially hazardous ingredients to the state Department of Health Serves, which in turn will

alert consumers. This law will utilize the California Proposition 65 toxicant list. One reproductive toxicant on the Prop 65 list, which is of concern to consumers, is di-n—butyl phthalate. The Breast Cancer Fund strongly supported the bill. The bill was opposed by individual cosmetic companies and the Cosmetic, Toiletry, and Fragrance Association, whose representative said they supported strong federal regulation by the FDA as opposed to a "state-by-state patchwork of rules". It should be noted that the FDA requires no pre-market testing of cosmetic products. Instead, an industry funded Cosmetic Review Board (CIR) performs a literature review and analysis of a priority list of ingredients. Since 1976 this expert panel has reviewed 1,286 ingredients and confirmed only 9 as unsafe.

Update: This bill passed and will become effective in January 2007.

**California AB 319:** AB 319 would prohibit the manufacture, sale, or distribution in commerce of any toy or child care article that is intended for use by a child under 3 years of age if that product contains bisphenol-A, contains DEHP, DBP, or BBP [phthalates] in concentrations exceeding 0.1%, or is intended for use by a child under 3 years of age if that product can be placed in the child's mouth, and contains DINP, DIDP, or DNOP in concentrations exceeding 0.1%. The bill would require manufacturers to use the least toxic alternative when replacing bisphenol-A and phthalates in their products and would prohibit manufacturers from replacing bisphenol-A and phthalates with certain carcinogens and reproductive toxicants. Jan. 31, 2006, From committee: Filed with the Chief Clerk pursuant to Joint Rule 56.

Update: The bill died pursuant to Art. IV, Sec. 10(c) of the Constitution.

**San Francisco, California**: In June of 2006 the San Francisco Board of Supervisors adopted an ordinance, based on the precautionary principle, that prohibits the sale, distribution or manufacture of toys and child care products intended for use by children under the age of 3 if they contain phthalates and bisphenol A. The ordinance does not include penalties for violations.

Update: In October of 2006, chemical manufacturers, toymakers, and retailers filed a lawsuit challenging the ordinance. Their suit argues that state law, including the California Hazardous Substances Act, pre-empts the San Francisco ordinance. The pending law, which was to have gone into effect on December 1, has been stayed pending the outcome of the lawsuit to be heard Jan. 8.

**Minnesota HB 3839** (SB 3379): Bisphenol-A and phthalates prohibited in products for young children. A bill for an act relating to consumer protection; prohibiting Bisphenol-A and Phthalates in products for young children; proposing coding for new law in Minnesota Statutes, chapter 325F. 03/22/2006 House Introduction and first reading, referred to Commerce and Financial Institutions/ 03/20/2006 Senate Referred to Commerce.

Update: The bill was introduced late in the session and did not garner much attention. It did not receive a hearing. Representative Clark plans to reintroduce the bill.

**New York AB 10115**: Add S392-a, Gen Bus L Prohibits the sale of toys or other articles intended for use by children under the age of four if such items contain phthalates; allows one

hundred twenty days for the toy industry to retool. 03/01/2006 referred to consumer affairs and protection.

Update: The lead sponsor, Assemblywoman Ginny Fields, will reintroduce the bill in January. The bill had several cosponsors.

Point of interest: Last year, the New York Public Interest Research Group (NYPIRG) commissioned laboratory tests of eight soft plastic toys labeled as "phthalate free"; six of the eight "phthalate-free" products were found to contain phthalates. This year NYPIRG again tested 10 toys labeled as "phthalate-free", 2 of the 10 toys labeled phthalate free contained detectable levels of phthalates.

**EU Restrictions on the use of phthalates in toys:** A temporary measure was first introduced in the EU in December 1999. The measure placed a temporary ban on the use of the DEHP, DBP, BBP, DINP, DIDP and DNOP in toys and childcare articles, designed to be placed in the mouth by children under the age of three years old.

Update: From January 17, 2007 additional restrictions on the use of phthalate plasticisers in toys will come into effect throughout the European Union. The phthalate plasticiser most commonly used in toys, Diisononyl phthalate (DINP), and the two phthalates diisodecyl phthalate (DIDP) and di-n-octyl phthalate (DNOP) can only be used in toys and childcare articles that cannot be placed in the mouth. The phthalate plasticisers di(2-ethylhexyl) phthalate (DEHP - sometimes also referred to a DOP), Di-n-butyl phthalate (DBP) and Butylbenzyl phthalate (BBP) will no longer be allowed in any children's toys or childcare articles.

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