Phthalates: Maine Chemicals of High Concern
A Review of the Science on Toxicity and Exposure

Deborah C. Rice, Ph.D.
March 2014

The purpose of this report is to review the latest science on several substances that are part of a large class of structurally similar chemicals known as phthalates. Seven of the phthalates have been formally designated as Chemicals of High Concern (CHCs) by the Maine Department of Environmental Protection under the authority of the Toxic Chemicals in Children's Products law, with concurrence by the Maine Center for Disease Control and Prevention based on an assessment of health effects and exposure. (For more information on Maine Chemicals of High Concern, see http://www.maine.gov/dep/safechem/highconcern/index.html). Evidence on toxicity and exposure for these seven CHCs is reviewed below, with an emphasis on human studies. Other phthalates that are not currently Maine CHCs may pose similar concerns but are beyond the scope of this review.

Phthalates are toxic to multiple organ systems in humans and animal models

Phthalates are a class of chemicals that may have multiple adverse health effects. It is well established that they are anti-androgenic compounds: that is, they interfere with the expression of the male sex hormone testosterone by influencing gene expression of enzymes and proteins involved in testosterone production. This may result in decreased fertility in adult males, as well as profound effects on the development of reproductive organs during prenatal development. During fetal development in mammals, testosterone is essential for the development of male sex organs. Phthalate exposure during this period produces a constellation of effects in male offspring in animal models, including abnormal penile development, abnormalities of the sperm-producing structures, hypospadias (urethral opening on the underside of the penis instead of the tip), decreased anogenital distance (a marker of feminization), and cryptorchidism (undescended testes). Similar effects have been observed in human studies associated with prenatal exposure to specific phthalates. Shorter anogenital distance is associated with poor semen quality in young men (Mendiola *et al*., 2011), as well as an increased risk for prostate cancer (Castaño-Vinyals *et al*., 2012). Effects on sexual development in both boys and girls are associated with phthalate exposure during childhood. Reproductive effects such as decreased gestational age and increased pregnancy loss have also been observed in human studies.

A critical issue is the potential for phthalate exposure to affect intellectual performance and other aspects of behavior. Prenatal phthalate exposure in humans is associated with poorer psychomotor development during infancy, poorer cognitive performance during childhood, and poorer social behavior. Not surprisingly, prenatal phthalate exposure is associated with less masculine play behavior in boys. Childhood phthalate exposure is associated with decreased IQ and vocabulary scores, and increased adverse scores for measures of attention, impulsivity, and ADHD behaviors. Phthalate levels were higher in children with autism spectrum disorders. Animal studies also document adverse behavioral effects following developmental phthalate exposure, and well as changes in brain

neurochemistry. Possible mechanisms include suppression of maternal thyroid hormone during pregnancy; interference with calcium signaling (important for communication between nerve cells); interference with receptors on cells that are involved in multiple processes during embryonic development; and interference with normal lipid metabolism, which is crucial for brain development (Miodovnik et al., 2014).

Phthalates also affect immune function. They produce specific pro-inflammatory effects in intact animals and *in vitro* (tissue culture or cell) systems. Phthalate exposure is associated with an increase in asthma, wheezing, and eczema in children, and an increase in inflammatory response in both children and adults.

Phthalate exposure is linked to obesity in both children and adults, as well as an increase in insulin resistance and diabetes in adults. Phthalate exposure is also associated with other adverse effects, including changes in thyroid hormone levels, increased blood pressure, increased risk of stroke, and an increased risk for endometriosis.

There is substantial evidence that phthalates on the Maine list of Chemicals of High Concern are toxic

Health effects of the specific phthalates on the Maine list of Chemicals of High Concern (CHC) are listed in Table 1. "Parent" refers to the chemical that is added to products. In animal studies, effects are linked to administration of the parent chemical at various doses. There is substantial evidence of toxicity for all of the CHC chemicals in animal studies[1]. (Presence on a national or international list of chemicals known to be toxic is a requirement for listing as a CHC.) In human studies, exposure to phthalates is assessed by the presence of one or more "metabolites," or breakdown products, usually measured in urine but occasionally in blood or breast milk. Therefore, for each CHC, effects may be linked to one or more of its metabolites. One of the CHCs, mono-*n*-butyl phthalate, is a metabolite of both benzyl butyl phthalate (BBP) and dibutyl phthalate (DBP) rather than a chemical that is added to products. Effects of this phthalate are therefore listed under the parent compounds.

The most studied phthalate in humans is di(2-ethylhexyl) phthalate (DEHP). Effects of DBP and BBP have also been assessed in multiple human studies. Effects of diethyl phthalate (DEP) have been determined in fewer studies, although adverse effects have been observed in a number of studies and summarized in extensive reviews. It is important to note that effects identified in a greater number of studies does not necessarily represent greater toxicity, but may reflect which metabolites were chosen for analysis by the investigators.

[1] Evidence for toxicity in animal studies relied on review articles for all but two of the CHCs; therefore each citation represents multiple studies. Additionally, endpoints that have not been the subject of review articles would not be included in the table, potentially including mechanistic studies. Most reviews did not include information on di-n-hexyl phthalate (DHP) and dicyclohexyl phthalate (DCHP); therefore the primary literature was searched for information on toxicity studies for these CHCs.

Most CHC phthalates are present in the majority of people in the United States

Metabolites of five of the seven phthalates on the CHC list have been detected in multiple epidemiological studies as evidenced by the health consequences listed in Table 1 (as have several phthalates not on the CHC list).

The most comprehensive source of information on the presence of these and other chemicals in the bodies of U.S. residents is a biomonitoring program by the U.S. Centers for Disease Control and Prevention (CDC) (CDC, 2013). The CDC samples thousands of individuals across the country in a strategy designed to yield data representative of the U.S. population. For phthalates (and most other chemicals) data are presented separately for children (6-11 years), adolescents (12-19 years), and adults, as well as totals for all males and females. Data for phthalates are available from 1999-2000 to 2009-2010. Metabolites of six of the seven CHCs are currently monitored by the CDC. The CDC analyzed more metabolites of the parent CHCs as well and other phthalates in recent years. Additionally, the CDC presumably does not monitor the metabolites of all the phthalates that are in use, particularly those put into production more recently. Therefore it is impossible to completely understand the pattern of phthalate exposure over the course of the years monitored by the CDC. Nonetheless, some conclusions may be drawn regarding relative exposure to specific subgroups of the population, as well exposure to the CHCs specifically.

Considering the sum of all urinary metabolites of the phthalates monitored by the U.S. CDC, females have higher levels in their bodies than males (Figure 1). Highest levels are found in children, with adolescents and adults having comparable urinary phthalate concentrations. These findings suggest that children and fetuses are at increased risk based simply on greater exposure, in addition to greater vulnerability as a consequence of increased sensitivity of developing organ systems to chemical exposure.

The CHC phthalate with the highest concentration of its metabolite monitored by the U.S.CDC is DEP (Figure 2). The metabolite of DEP increased slightly from 1999-2000 to 2003-2004, and decreased thereafter. The next highest concentrations of metabolites are those of DEHP. Four metabolites of DEHP are monitored by the U.S.CDC. Urinary concentrations of these metabolites increased from 1999-2000 to 2005-2006, and then decreased. A majority of people in the U.S. also have measurable levels of metabolites of BBP and DBP in their bodies. Metabolites of BBP and DBP generally decreased over the years for which data are available.

The metabolite of DCHP is monitored by the U.S.CDC, and is found in a relatively smaller proportion of people. DHP is not monitored by the U.S.CDC. No human health studies were identified for either of these phthalates. Lack of data does not signify that these compounds are not responsible for adverse effects in humans. This is particularly relevant for DHP, for which levels in humans are apparently unknown.

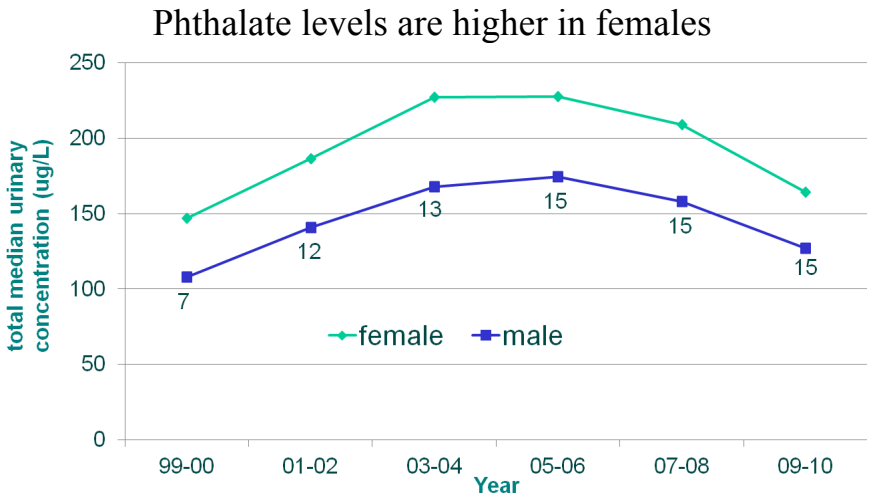
Comparing the pattern of metabolites for CHCs versus other phthalates reveals that whereas the concentrations of the CHC metabolites have decreased across recent years, concentrations of the metabolites of the newer phthalates are increasing (Figure 3). However, the concentrations of CHC metabolites in individuals are still about three times higher than those of other measured metabolites. As mentioned above, these data undoubtedly do not represent the totality of phthalate metabolites in individuals in the United States at present.

An important question is whether the effects observed in the epidemiological studies were observed when total phthalate concentrations were at their peak. Figure 4 depicts the times at which cohorts were constituted for reproductive, behavioral, and other outcomes in studies in which the time frame of when individuals were recruited into the study (and therefore phthalate levels were measured) are stated in the manuscript. The curve represents the seven metabolites that were measured in all years from 1999-2000 to 2009-2010 by the CDC; this was done in an attempt to best represent the pattern of exposure across years. It can be seen that in more than half the studies, individuals were recruited in years in which phthalate concentrations were decreasing as measured by the CDC. This provides evidence that despite some apparent decline in phthalate exposure (although whether this is in fact true is not clear), these levels still represent a risk to human health.

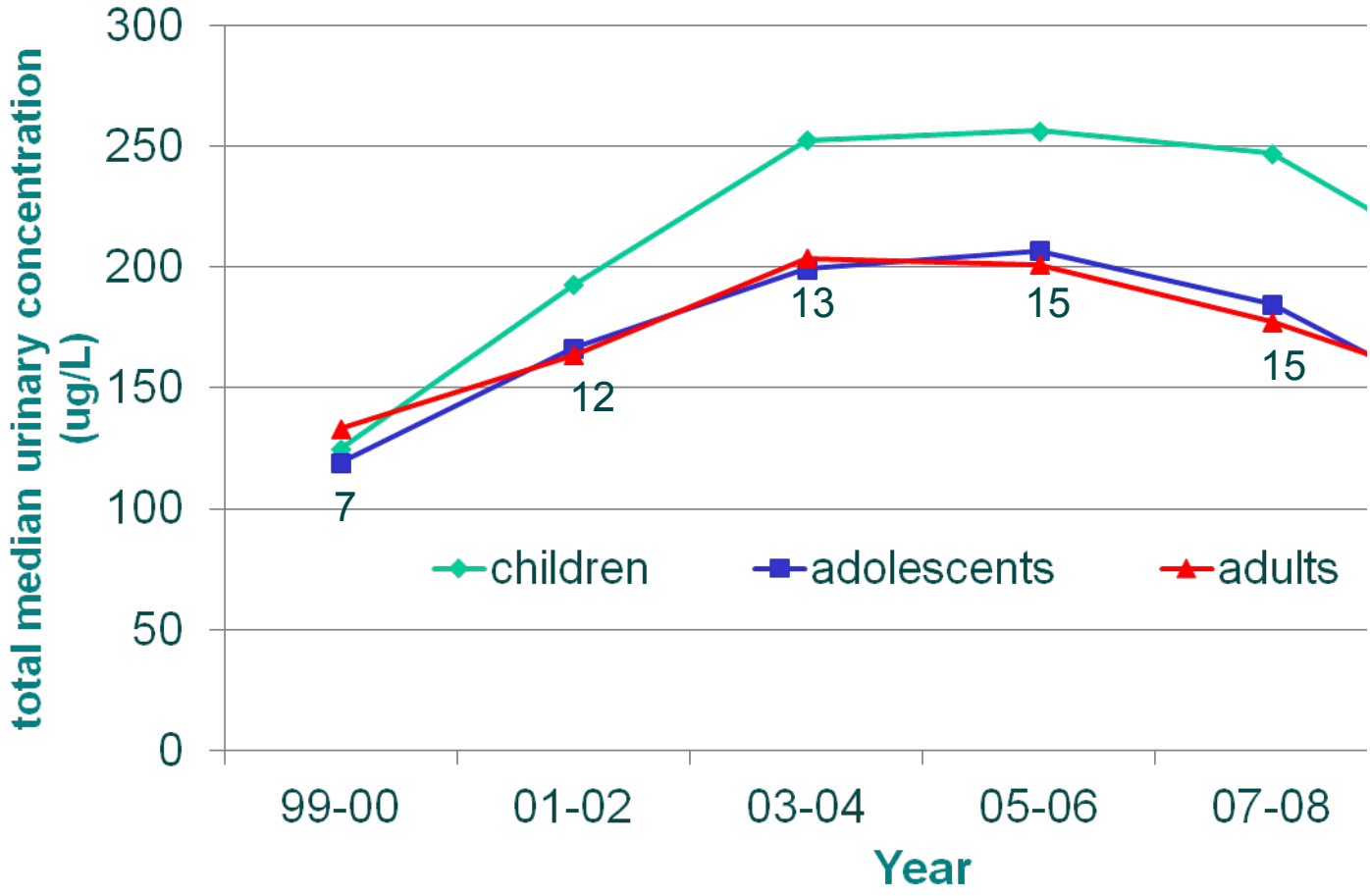
Phthalates and other environmental contaminants cannot be considered individually

Each individual has multiple phthalates in his or her body, as well as multiple other chemicals that may affect the same health outcomes as the phthalates. As an example, the sum of the metabolites of several phthalates was associated with adverse effects in some epidemiological studies listed in Table 1. Phthalates have additive effects in animal models on male reproductive malformations during development, and mixtures of phthalates and other anti-androgenic compounds also have a cumulative effect on male reproductive tract development (Rider *et al*., 2010; Howdeshell *et al*., 2008; Martino-Andrade and Chahoud, 2010). For example, DBP + DEHP act in an additive manner to produce adverse effects on several parameters of male sexual development, as well as testosterone production and gene expression. Combinations of BBP, DBP, DEHP, and DiBP (the last not a CHC) also had additive effects on fetal testosterone production. Mixtures of BBP, DBP, and DEHP with four anti-androgenic agricultural chemicals produced cumulative effects on anogenital distance, depression of androgen-dependent organ weights, retention of nipples by male rats (which is abnormal and represents a feminization), and induction of reproductive malformations. These and other studies highlight the danger of considering any chemical in isolation, since all of us carry dozens of chemicals in our bodies that may together produce adverse effects that may not be produced by a specific body burden of each chemical individually.

Figure 1. Average concentrations of phthalates in urine of individuals in the U.S.



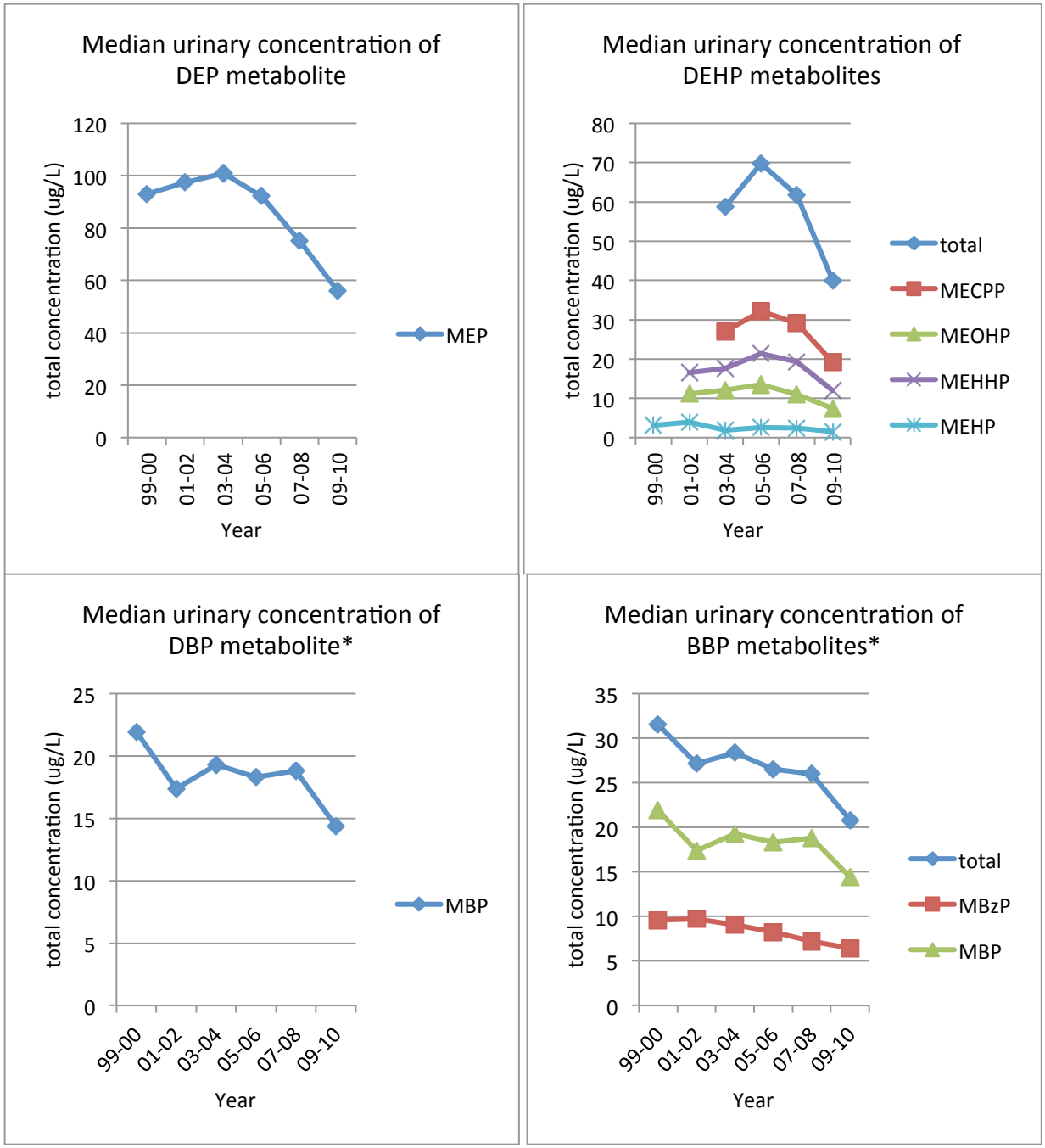
Phthalate levels are highest in children



Based on the total phthalate metabolites monitored by the U.S. Centers for Disease Control and Prevention.

Numbers associated with each year represent the total number of metabolites monitored in that year.

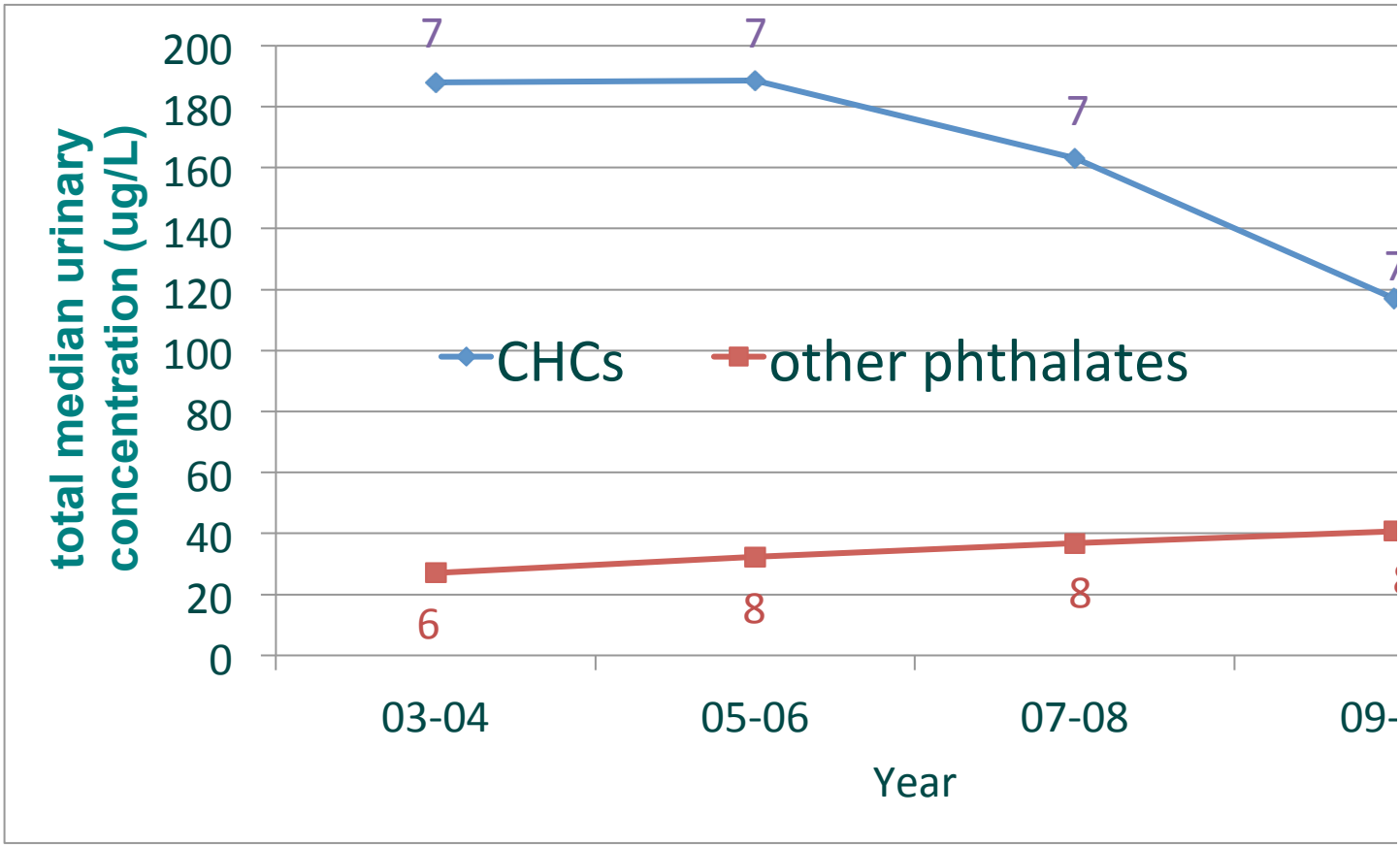
Figure 2. Metabolites of CHC phthalates in urine of individuals in the U.S.



*** MBP is a metabolite of both DBP and BBP. Since the relative concentrations for each parent chemical are unknown, the total concentration of MBP was apportioned equally between the two parent compounds.**

Data from the U.S. Centers for Disease Control and Prevention

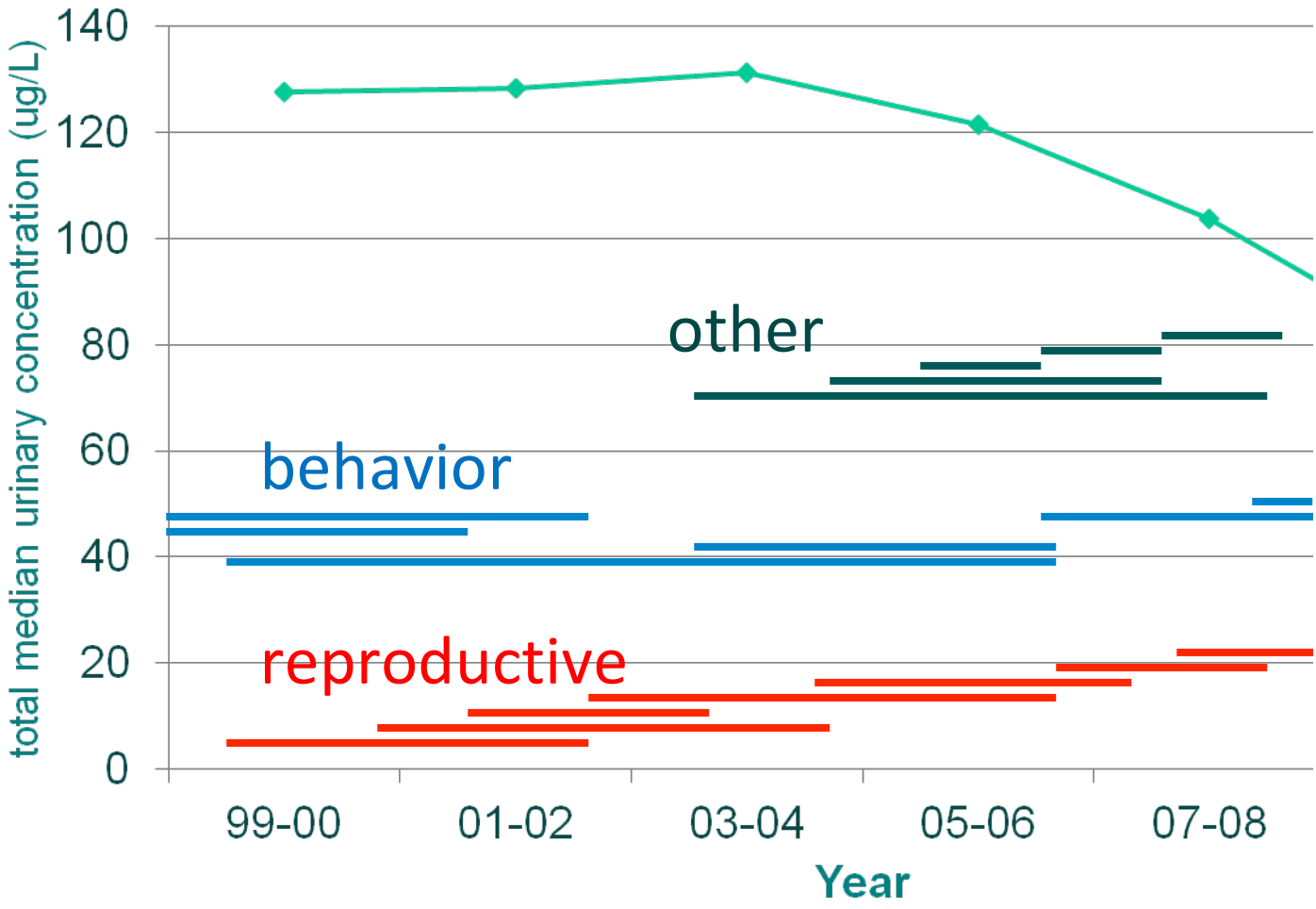
Figure 3. Concentration of CHCs and other phthalates in the U.S. population



Numbers on each data point represent the number of metabolites analyzed in that year

Data from the U.S. Centers for Disease Control and Prevention

Figure 4. Time period when cohorts were recruited for epidemiological studies assessing specific outcomes



Horizontal lines represent the years over which subjects were recruited into each study and therefore when concentrations of phthalates were measured.

Graph data points represent the total of the seven metabolites that were measured over all years. Data from the U.S. Centers for Disease Control and Prevention.

Evidence of Toxicity of MeCHC Phthalates from Animal and Human Studies

CAS # 117-81-7 parent: di (2-ethylhexyl) phthalate (DEHP)
metabolites: mono-2-ethylhexyl phthalate (MEHP)
mono-2-ethyl-5 hydroxyhexyl phthalate (MEHHP)
mono-2-ethyl-5 oxyhexyl phthalate (MEOHP)
mono-2-ethyl-5-carboxypentyl phthalate (MECPP)

Animal Studies

prenatal exposure

sexual development

abnormal penile development, agenesis of epididymus, hypospadias, testicular malformations, cryptorchidism	Howdeshell *et al*., 2008, review; Witorch and Thomas, 2010, review; Talsness *et al*., 2009, review
inhibition of testosterone in Leydig cells; MEHP: increased testosterone in mouse fetal testes	Witorch and Thomas, 2010, review; Talsness *et al*., 2009, review
impaired sexual performance in males during adulthood	Miodovnik *et al*., 2014, review

brain and behavior

impaired motor development	Miodovnik *et al*., 2014, review

developmental exposure

sexual development

decreased vaginal opening and first estrus	Martino-Andrade and Chahoud, 2010, review

brain and behavior

increased motor activity, increased anxiety behavior in males, changes in neurotransmitter systems	Miodovnik *et al*., 2014, review

adult exposure

reproduction

prolonged estrus cycles, decreased estradiol levels and absence of ovulation, decreased fertility	Martino-Andrade and Chahoud, 2010, review
adverse effects on reproductive organs and hormones, ovulation, fertility, and pregnancy in females	Kay *et al*., 2013, review

immune function

effect on immune cells *in vitro*	Bornehag and Nanberg, 2010, review
increased antibody response *in vivo*	Tsai *et al*., 2012, review
increased pulmonary inflammation related to DEHP in dust	He *et al.,* 2013

cancer

tumors in several organs	Wang *et al*., 2012, review

cancer and DNA damage in multiple tissues and species, mutagenic and non-mutagenic mechanisms	Caldwell 2012, review
positive (adverse) *in vitro* chromosome aberration test	Wang *et al*., 2012, review

Human Studies

prenatal exposure

sexual development

increased SHBG (sex hormone binding globule) in males (lactational exposure)	Main *et al*., 2006
increased hypospadias	Choi *et al*., 2012
decreased anogenital distance, decreased penile size, delayed testicular descent	Swan *et al*., 2005, 2008

behavior

adverse behavioral development in boys at 6 months	Kim *et al*,. 2011
sum high molecular weight (MBzP + DEHP metabolites + MCPP), decreased attending to stimuli (orienting), quality of alertness in girls at 5 days of age	Engel *et al*., 2009
poorer reflexes at 5 weeks in boys	Yolton *et al*., 2011
decreased masculine play in boys	Swan *et al*., 2009

development

decreased gestational age at birth, male and female	Swan *et al*., 2008, review section of paper
increased preterm birth	Meeker *et al*., 2009

childhood exposure

sexual development

increased pubarche in girls	Frederiksen *et al*., 2012
pubertal gynecomastia in boys	Durmaz *et al*., 2010
premature thelarche in girls	Colón *et al*., 2000
sum high molecular weight (MBzP + DEHP metabolites + MCPP) delayed pubic hair development in girls	Wolff *et al*., 2010
precocious puberty in girls; increased volume of uteruses and ovaries in precocious girls	Qiao *et al*., 2011, cited in Jurewicz and Hanke, 2011, review

behavior

decreased vocabulary scores ; decreased IQ	Cho *et al*., 2011
increased ADHD scores	Kim *et al*., 2009
increase in children with autism spectrum disorders	Testa *et al*., 2012

metabolism

sum DEHP metabolites, increased body mass index; sum high molecular weight (MECPP + DEHP metabolites + MBzP),	Teitelbaum *et al*., 2012

increased BMI and waist circumference	
decreased growth factor and growth 4-9 year old boys	Boas *et al*., 2010
interacts with PPARs, mechanism for obesity	Desvergne *et al*., 2009
immune function	
increased asthma markers	Tsai *et al*., 2012, review
increased asthma, wheezing, eczema related to house dust in girls and boys	Swan *et al*., 2008, review section of paper; Jurewicz and Hanke, 2011, review
wheeze related to house dust	Callesen *et al*., 2013
other effects	
increased blood pressure	Trasande *et al*., 2013
increased thyroid levels in adolescents	Meeker and Ferguson, 2011
adult exposure	
reproduction	
decreased testosterone in men	Joensen *et al*., 2012
increased pregnancy loss	Toft *et al*., 2012
increased endometriosis	Buck Louis *et al*., 2013
other endocrine effects	
decreased thyroid hormone levels in males	Meeker and Ferguson, 2011; Meeker *et al*., 2007
decreased thyroid hormone levels in pregnant women	Huang *et al*., 2007
metabolism	
increased waist circumference in males	Stalhut *et al*., 2007
increased LDL cholesterol in elderly	Olsen *et al*., 2013
immune function	
markers for immune function and *in vitro* markers under some conditions but not others; inhaled DEHP results in positive (adverse) response	Kimber *et al*., 2010, review; Tsai *et al*., 2012, review
effects on genes involved in immune response; also non-genomic effects	Tsai *et al*., 2012, review
in vitro inflammatory effects	Bornehag and Nanberg 2010, review
cancer	
increased sperm DNA damage; decreased sperm morphology	Swan *et al*., 2008, review section of paper
DNA damage, *in vitro* studies mutagenic and nonmutagenic changes	Caldwell 2012, review

CAS# 84-74-2 parent: dibutyl phthalate (DBP)
CAS# 131-70-4 metabolite: mono-*n*-butyl phthalate (MBP) (also a Maine CHC)

Animal Studies

prenatal exposure

sexual development

abnormal penile development, agenesis of epididymus, hypospadias, testicular malformations, cryptorchidism	Howdeshell *et al*., 2008, review; Talsness *et al*., 2009, review; Witorch and Thomas, 2010, review
impaired sexual performance in males in adulthood	Miodovnik *et al*., 2014, review

brain and behavior

impaired motor development and learning in males	Miodovnik *et al*., 2014, review

developmental exposure

sexual development

inhibition of testosterone	Moody *et al*., 2013
change in testosterone production and Leydig cells in marmosets	Talsness *et al*., 2009, review
delayed puberty in females	Lyche *et al*., 2009, review

brain and behavior

increased motor activity, changes in and neurotransmitter levels and receptors	Miodovnik *et al*., 2014, review

adult exposure

reproduction

decreased fertility, mid-gestation abnormalities, increased progesterone, decreased estradiol in females	Martino-Andrade and Chahoud, 2010, review; Lyche *et al*., 2009, review; Kay *et al*., 2013, review

immune function

effects on immune cells *in vitro*	Bornehag and Nanberg, 2010, review
increased antibody response *in vivo* and *in vitro*	Tsai *et al*., 2012, review

cancer

positive (adverse) genetic mutation test	Wang *et al*., 2012, review

Human Studies

prenatal exposure

sexual development

decreased anogenital distance in boys	Swan *et al*., 2005, 2008
decreased anogenital distance in females	Jurewicz and Hanke, 2011

increased SHBG in males; increased ratio of lutinizing hormone to testosterone in males	Main *et al*., 2006
decreased testosterone in males (lactational exposure)	Swan 2008, review section of paper
development	
increased preterm birth	Meeker *et al*., 2009
behavior	
motor delay, clinically withdrawn behavior, poorer cognitive score at 3 years	Whyatt *et al*., 2012
sum of low molecular weight (MMP + MEP + MBP + MiBP), higher scores for measures of conduct or attention deficit disorder	Engel *et al*., 2010
sum of low molecular weight (MMP + MEP + MBP + MiBP) sex-specific pattern for orienting, motor performance at 5 days of age	Engel *et al*., 2009
decreased masculine play in boys	Swan *et al*., 2009
less masculine behavioral score in boys	Meeker and Ferguson, 2011
poorer social behavior at 7-9 years	Miodovnik *et al*., 2011
immune function	
increased inflammatory response	Tsai *et al*., 2012, review
childhood exposure	
sexual development	
sum (MBP + MBzP), delayed pubic hair development in girls	Frederiksen *et al*., 2012
sum low molecular weight (MEP + MiBP + MBP), delayed pubic hair and breast development in girls	Wolff *et al*., 2010
increased DBP levels in precocious girls: increased volume of uteruses and ovaries in girls with precocious puberty	Qiao *et al*., 2007, cited in Jurewicz and Hanke, 2011
behavior	
decreased vocabulary scores	Cho *et al*., 2010
more errors on a test of attention and impulsivity, higher ADHD score	Kim *et al*., 2009
immune function	
eye symptoms related to DBP in dust	Hsu *et al*., 2011
metabolism	
sum (MEP + MBP + MiBP), increased BMI and waist circumference	Teitelbaum *et al*., 2012
adult exposure	
reproduction	

decreased sperm motility and concentration; decreased testosterone and increased ratio of lutinizing hormone to testosterone in males	Swan *et al*., 2008, review section of paper
poor sperm quality	Witorch and Thomas, 2010, review
decreased sperm motility	Lyche *et al*., 2009, review
increased endometriosis	Buck Louis *et al*., 2013
decreased thyroid hormone levels in pregnant women	Huang *et al*., 2007
metabolism	
increased waist circumference in males	Stalhut *et al*., 2007
increased insulin resistance	Swan *et al*., 2008, review section of paper
other effects	
increased risk of stroke	Shiue, 2013
decreased pulmonary function	Swan *et al*., 2008, review section of paper

CAS# 85-68-7 parent: benzyl butyl phthalate (BBP)
CAS# 131-70-4 metabolite: mono-*n*-butyl phthalate (MBP) (also a Maine CHC)
mono-benzyl phthalate (MBzP)

Animal Studies

sexual development

prenatal exposure - abnormal penile development, agenesis of epididymus, hypospodias, testicular malformations, cryptorchidism	Howdeshell *et al*., 2008, review; Martino-Andrade and Chahoud, 2010, review; Witorch and Thomas, 2010, review

brain and behavior

postnatal exposure - changes in social behavior, changes in brain enzyme	Miodovnik *et al*., 2014, review

reproduction

adverse effects on fertility (females) and pregnancy	Kay *et al*., 2013, review

immune function

increased antibody respond *in vivo* and *in vitro*	Tsai *et al*., 2012, review

cancer

positive (adverse) on chromosome aberration test	Wang *et al*., 2012, review

Human Studies - MBP

prenatal exposure

sexual development

decreased anogenital distance in males	Swan *et al*., 2005, 2008
decreased testosterone levels in males (lactational exposure)	Swan *et al*., 2008, review section of paper
decreased anogenital distance in females	Jurewicz and Hanke, 2011
increased SHBG and increased ratio of lutinizing hormone to testosterone in males	Main *et al*., 2006

development

increased preterm birth	Meeker *et al*., 2009

behavior

motor delay, clinically withdrawn behavior, poorer cognitive score at 3 years	Whyatt *et al*., 2012

sum of low molecular weight (MMP + MEP + MBP + MiBP), higher scores for measures of conduct or attention deficit disorder	Engel *et al*., 2010
sum of low molecular weight (MMP + MEP + MBP + MiBP) sex-specific pattern for orienting, motor performance at 5 days of age	Engel *et al*., 2009
less masculine behavioral score in boys	Meeker and Ferguson, 2011
decreased masculine play in boys	Swan *et al*., 2009
poorer social behavior at 7-9 years	Miodovnik *et al*., 2011
immune function	
increased inflammatory response	Tsai *et al*., 2012, review
childhood exposure	
sexual development	
sum (MBP + MBzP), delayed pubic hair development in girls	Frederiksen *et al*., 2012
sum low molecular weight (MEP + MiBP + MBP), delayed pubic hair and breast development in girls	Wolff *et al*., 2010
increased DBP levels in precocious girls: increased volume of uteruses and ovaries in girls with precocious puberty	Qiao *et al*., 2007, cited in Jurewicz and Hanke, 2011
increased errors in test of attention and impulsivity, higher ADHD score	Kim *et al*., 2009
decreased vocabulary scores	Cho *et al*., 2010
immune function	
rhinitis related to BBP in dust	Hsu *et al*., 2011
metabolism	
sum (MEP + MBP + MiBP), increased BMI and waist circumference	Teitelbaum *et al*., 2012
adult exposure	
reproduction	
decreased sperm motility and concentration; decreased testosterone, increased ratio of lutinizing hormone to testosterone in males	Swan *et al*., 2008, review section of paper
poor sperm quality	Witorch and Thomas, 2010, review
decreased sperm motility	Lyche *et al*., 2009, review
increased endometriosis	Buck Louis *et al*., 2013
metabolism	
increased waist circumference in males	Stalhut *et al*., 2007
increased insulin resistance	Swan *et al*., 2008, review section of paper

other effects

increased risk of stroke	Shiue, 2013
decreased pulmonary function	Swan *et al*., 2008, review section of paper

Human Studies - MBzP

prenatal exposure

behavior

motor delay, clinically withdrawn and internalizing behavior at 3 years	Whyatt *et al*., 2012
sum (MBzP + DEHP metabolites + MCPP), decreased attending to stimuli (orienting), quality of alertness in girls at 5 days of age	Engel *et al*., 2009

childhood exposure

sexual development

sum (MBP + MBz), delayed pubic hair development in girls	Frederiksen *et al*., 2012

immune function

rhinitis related to BBP in dust	Hsu *et al*., 2011

adult exposure

reproduction

decreased sperm concentration; decreased follicular stimulating hormone in males	Swan *et al*., 2008, review section of paper

metabolism

increased waist circumference; increased insulin resistance	Stalhut *et al*., 2007

immune function

allergic symptoms and sensitization	Hoppen *et al*., 2013
rhinitis and eczema	Jurewicz and Hanke, 2011, review

CAS# 84-66-2 parent: diethyl phthalate (DEP)
metabolite: monoethyl phthalate (MEP)

Animal Studies

reproduction

adverse effects on female reproductive system	Kay *et al*., 2013, review

Human Studies

prenatal exposure

sexual development

decreased anogenital distance	Swan *et al*., 2005, 2008
increased SHBG and increased ratio of lutinizing hormone to testosterone in males	Main *et al*., 2006

behavior

poorer social behavior at 7-9 years	Miodovnik *et al*., 2011
low molecular weight(sum (MMP + MEP + MBP + MiBP), sex-specific pattern for orienting, motor performance at 5 days of age	Engel *et al*., 2009
low molecular weight sum (MMP + MEP + MBP + MiBP), higher scores for measures of conduct or attention deficit disorder	Engel *et al*., 2010

childhood exposure

metabolism

MEP alone and sum (MEP + MBP + MiBP), increased BMI and waist circumference	Teitelbaum *et al*., 2012

other endocrine effects

decreased thyroid hormone in 4-9 year old girls	Boas *et al*., 2010

adult exposure

reproduction

DNA damage in sperm	Witorch and Thomas, 2010, review; Swan *et al*., 2008, review section of paper
decreased sperm motility, reduced ratio of lutinizing hormone to free testosterone in males	Lyche *et al*., 2009, review; Swan *et al*., 2008, review section of paper

metabolism

increased insulin resistance	Swan *et al*., 2008, review section of paper
increased diabetes in elderly	Lind *et al*., 2012
increased waist circumference in males	Stalhut *et al*., 2007

immune function

increased inflammatory response	Tsai *et al*., 2012, review

other effects

increased blood pressure in elderly	Olsen *et al*., 2013

CAS# 84-61-7 parent: dicyclohexyl phthalate (DCHP)
metabolite: monocyclohexyl phthalate (MCHP)

Animal Studies

prenatal exposure

sexual development

decreased anogenital distance in females	Saillenfait *et al*., 2009a
decreased testosterone at puberty, abnormality in reproductive organs	Ahbab *et al*., 2013a
genotoxic effects on testicular cells at all life stages	Ahbab *et al*., 2013b
multiple effects on sexual development in males	Yamasaki *et al*., 2009

development

growth retardation	Saillenfait *et al*., 2009a

developmental exposure

sexual development

2-generation reproductive study: reproductive changes in parent generation, some changes in reproductive organs of male offspring, effects on reproduction largely negative	Hoshino *et al*., 2005

development

"developmental toxicant"	Kay *et al*., 2013, review

behavior

hyperactivity; down regulation of dopamine D4 receptor, changes in gene expression (regulation of brain chemical)	Ishido *et al*., 2004

reproductive effects

"reproductive toxicant" in females	Kay *et al*., 2013, review
2-generation reproductive study: reproductive changes in parent generation, some changes in reproductive organs of male offspring, effects on reproduction largely negative	Hoshino *et al*., 2005

in vitro effects

brain function

disruption of calcium signaling of brain receptor (nicotinic acetylcholine receptor)	Lu *et al*., 2004

reproduction

effects on estrogen response	Hong *et al*., 2005
binds to estrogen receptor	Nakai *et al*., 1999

metabolism

disruption of glucocorticoid regulation	Zhao *et al*., 2010

other endocrine effects

inhibition of thyroid hormone synthesis pathways	Sugiyama *et al*., 2005
immune function	
effects on immune cell response	Bornehag and Nanberg, 2010, review
other effects	
inhibition of specific kidney enzymes	Ohshima *et al*., 2005

Human Studies

no epidemiological studies identified

monitored by CDC

detected in < 16% of U.S. population in 2000 Silva *et al*., 2004

CAS# 84-75-3 parent: di-*n*-hexyl phthalate (DHP)
metabolite: mono-*n*-hexyl phthalate

Animal Studies

prenatal exposure

sexual development

adverse developmental effects, decreased anogenital distance in males, undescended testes	Saillenfait *et al*., 2009a
severe malformation of reproductive tract in adulthood, including undeveloped and undescended testes, hypospadias	Saillenfait *et al*., 2009b
decreased testosterone at puberty in males, abnormalities in reproductive organs	Ahbab *et al*., 2013a
genotoxic effects on testicular cells at all life stages	Ahbab *et al*., 2013b
decreased testosterone	Saillenfait *et al*., 2013

metabolism

altered gene expression for cholesterol transport and steroid synthesis	Saillenfait *et al*., 2013

reproduction

"is a reproductive and developmental toxicant"	National Toxicology Program, 2003, review
"reproductive toxicant" in females	Kay *et al*., 2013, review

development

"is a reproductive and developmental toxicant"	National Toxicology Program, 2003, review

Human Studies

no epidemiological studies identified

not monitored by CDC

no biomonitoring studies identified

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