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

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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. (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-β-butyphthalate, 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.

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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 higher in females

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

inhibition of testosterone in Leydig cells; MEHP: increased testosterone in mouse fetal testes

impaired sexual performance in males during adulthood

*brain and behavior*

impaired motor development

**developmental exposure**

*sexual development*

decreased vaginal opening and first estrus

*brain and behavior*

increased motor activity, increased anxiety behavior in males, changes in neurotransmitter systems

**adult exposure**

*reproduction*

prolonged estrus cycles, decreased estradiol levels and absence of ovulation, decreased fertility

adverse effects on reproductive organs and hormones, ovulation, fertility, and pregnancy in females

*immune function*

effect on immune cells in vitro

increased antibody response in vivo

increased pulmonary inflammation related to DEHP in dust

*cancer*

tumors in several organs

Howdeshell *et al.*, 2008, review; Witorch and Thomas, 2010, review; Talsness *et al.*, 2009, review

Witorch and Thomas, 2010, review; Talsness *et al.*, 2009, review

Miodovnik *et al.*, 2014, review

Martino-Andrade and Chahoud, 2010, review

Miodovnik *et al.*, 2014, review

Martino-Andrade and Chahoud, 2010, review

Kay *et al.*, 2013, review

Bornehag and Nanberg, 2010, review

Tsai *et al.*, 2012, review

He *et al.*, 2013

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  Colòn 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

interacts with PPARs, mechanism for obesity

*immune function*

increased asthma markers

increased asthma, wheezing, eczema related to house dust in girls and boys

wheeze related to house dust

*other effects*

increased blood pressure

increased thyroid levels in adolescents

*adult exposure*

*reproduction*

decreased testosterone in men

increased pregnancy loss

increased endometriosis

*other endocrine effects*

decreased thyroid hormone levels in males

decreased thyroid hormone levels in pregnant women

*metabolism*

increased waist circumference in males

increased LDL cholesterol in elderly

*immune function*

markers for immune function and in vitro markers under some conditions but not others; inhaled DEHP results in positive (adverse) response

effects on genes involved in immune response; also non-genomic effects

*in vitro inflammatory effects*

*cancer*

increased sperm DNA damage; decreased sperm morphology

DNA damage, in vitro studies mutagenic and nonmutagenic changes

Boas et al., 2010

Desvergne et al., 2009

Tsai et al., 2012, review

Swan et al., 2008, review section of paper; Jurewicz and Hanke, 2011, review

Callesen et al., 2013

Trasande et al., 2013

Meeker and Ferguson, 2011

Joensen et al., 2012

Toft et al., 2012

Buck Louis et al., 2013

Meeker and Ferguson, 2011; Meeker et al., 2007

Huang et al., 2007

Stalhut et al., 2007

Olsen et al., 2013

Kimber et al., 2010, review; Tsai et al., 2012, review

Tsai et al., 2012, review

Bornehag and Nanberg 2010, review

Swan et al., 2008, review section of paper

Caldwell 2012, review
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 luteinizing 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

poor sperm quality

decreased sperm motility

increased endometriosis

decreased thyroid hormone levels in pregnant women

*metabolism*

increased waist circumference in males

increased insulin resistance

*other effects*

increased risk of stroke

decreased pulmonary function

Swan *et al.*, 2008, review section of paper

Witorch and Thomas, 2010, review

Lyche *et al.*, 2009, review

Buck Louis *et al.*, 2013

Huang *et al.*, 2007

Stalhut *et al.*, 2007

Swan *et al.*, 2008, review section of paper

Shiue, 2013

Swan *et al.*, 2008, review section of paper
CAS# 85-68-7  parent: benzyl butyl phthalate (BBP)
CAS# 131-70-4  metabolite: mono-\textit{n}-butyl phthalate (MBP) (also a Maine CHC)
mono-benzyl phthalate (MBzP)

**Animal Studies**

\textit{sexual development}

prenatal exposure - abnormal penile development, agenesis of epididymus, hypospadias, testicular malformations, cryptorchidism

\textit{brain and behavior}

postnatal exposure - changes in social behavior, changes in brain enzyme

Howdeshell \textit{et al}., 2008, review; Martino-Andrade and Chahoud, 2010, review; Witorch and Thomas, 2010, review

Miodovnik \textit{et al}., 2014, review

\textit{reproduction}

adverse effects on fertility (females) and pregnancy

\textit{immune function}

increased antibody respond \textit{in vivo} and \textit{in vitro}

Tsai \textit{et al}., 2012, review

\textit{cancer}

positive (adverse) on chromosome aberration test

Wang \textit{et al}., 2012, review

**Human Studies - MBP**

\textit{prenatal exposure}

\textit{sexual development}

decreased anogenital distance in males

decreased testosterone levels in males (lactational exposure)

decreased anogenital distance in females


Swan \textit{et al}., 2008, review section of paper

Jurewicz and Hanke, 2011

Main \textit{et al}., 2006

\textit{development}

increased preterm birth

Meeker \textit{et al}., 2009

\textit{behavior}

motor delay, clinically withdrawn behavior, poorer cognitive score at 3 years

Whyatt \textit{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

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<th>Human Studies - MBzP</th>
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<td>prenatal exposure</td>
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<td>behavior</td>
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<td>rhinitis related to BBP in dust</td>
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<td>reproduction</td>
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<td>decreased sperm concentration; decreased follicular stimulating hormone in males</td>
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<th>metabolism</th>
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<td>increased waist circumference; increased insulin resistance</td>
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<th>immune function</th>
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<td>allergic symptoms and sensitization</td>
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<td>rhinitis and eczema</td>
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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
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

*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
**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
References


Ahbab, M.A., Undeger, U., Barlas, N., Basaran, N. In utero exposure to dicyclohexyl and di-n-hexyl phthalate possess genotoxic effects on testicular cells of male rats after birth in the comet and TUNEL assays. Hum Exp Toxicol 2013b


National Toxicology Program. NTP-CERHR monograph on the potential human reproductive and developmental effects of di-n-hexyl phthalate (DnHP). 2003.


