Toxic Effects of the Easily Avoidable Phthalates and Parabens

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Abstract
Some environmental toxins like DDT and other chlorinated compounds accumulate in the body because of their fat-soluble nature. Other compounds do not stay long in the body, but still cause toxic effects during the time they are present. For serious health problems to arise, exposure to these rapidly-clearing compounds must occur on a daily basis. Two such classes of compounds are the phthalate plasticizers and parabens, both of which are used in many personal care products, some medications, and even foods and food preservation. The phthalates are commonly found in foods and household dust. Even though they have relatively short half-lives in humans, phthalates have been associated with a number of serious health problems, including infertility, testicular dysgenesis, obesity, asthma, and allergies, as well as leiomyomas and breast cancer. Parabens, which can be dermally absorbed, are present in many cosmetic products, including antiperspirants. Their estrogenicity and tissue presence are a cause for concern regarding breast cancer. Fortunately, these compounds are relatively easy to avoid and such steps can result in dramatic reductions of urinary levels of these compounds.
(Altern Med Rev 2010;15(3):190-196)

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Phthalates

With over 18 billion pounds of phthalates used each year, they represent one of the world's high production chemical families. Phthalates, in numerous consumer items, provide flexibility and resilience to plastic products. Di-ethylhexyl phthalate (DEHP) is the most commonly used plasticizer for polyvinyl chloride (PVC); the production volume of DEHP alone in 1999 was estimated to be two million tons. Phthalates are found in adhesives, automotive plastics, detergents, flooring, raincoats, personal care products (cosmetics, shampoos, fragrances, etc.), plastic bags, garden hoses, building materials, household furnishings, pharmaceuticals, nutritional supplements, children's toys, food packaging, cleaning material, insecticides, and other common compounds. Phthalates are also used to manufacture the 500 million pairs of disposable medical examination and sterile surgical vinyl gloves that are produced every year. Typically, the more flexible the plastic, the higher the amount of phthalates in the product. Because phthalates are not chemically bound to the plastics to which they are added, they can easily be released into the environment. This includes leaching and release into air, dust, and food. Since phthalates are rapidly excreted from the body, their presence in the urine indicates current exposure.

The CDC 4th National Report lists urinary levels (mcg/g creatinine) of several common phthalates (Table 1).[1]

A study of 100 pregnant women in the Netherlands examined urinary levels of a number of phthalate metabolites.[2] Table 2 illustrates some of their findings, presented in the same order as Table 1 from the CDC 4th Report.

Types and Sources of Phthalates

A comparison of the two studies shows that multiple phthalate metabolites are present in two different human populations. Note that the levels of these metabolites vary between U.S. and Rotterdam women. Expectant mothers from the Netherlands have much higher levels of mono-isobutyl phthalate (MiBP) and mono-n-butyl phthalate (MnBP). MiBP is the metabolite of di-isobutyl phthalate (DIBP) and MnBP is the metabolite of di-n-butyl phthalate (DNBP), and are most commonly used in PVC plastics, latex products, cosmetics, personal care products, cellulose plastics, and as solvents for some dyes. Mono-ethyl phthalate (MEP), the metabolite found in the highest levels in both studies, is the

Key words: phthalate, paraben, toxic, toxicity, toxin, plasticizer, environment, environmental

Table 1. Urinary Levels of Several Common Phthalates (mcg/g creatinine)

Compound	Geometric mean	50th percentile	75th percentile	90th percentile	95th percentile
Mono benzyl phthalate	12.9	12.6	24.6	46.0	70.0
Mono isobutyl phthalate	3.57	3.57	6.21	10.9	
Mono n-butyl phthalate	19.8	19.3	33.9	59.0	91.6
Mono ethyl phthalate	181	153	452	1,110	2,040
Mono-2-ethylhexyl phthalate	2.20	1.89	4.31	10.8	25.4
Mono-(2-ethyl-5-hydroxyhexyl) phthalate	20.4	17.7	35.8	93.5	182
Mono-(2-ethyl-5-oxyhexyl) phthalate	13.6	12.1	24.3	63.0	118
Mono-(2-ethyl-5-carboxypentyl) phthalate	32.6	27.0	54.6	139	251
Mono methyl phthalate	<LOD	1.53	3.45	7.95	13.5
Mono (3-carboxypropyl) phthalate	2.74	2.60	4.39	7.70	10.7

LOD=level of detection

metabolite of di-ethyl phthalate (DEP), which is primarily found in cosmetics and personal care products. Thus, it appears that the majority of phthalate metabolites in the urine of both populations came from personal care products and cosmetics. A report from the Environmental Working Group and Healthcare Without Harm revealed that DEP and di-butyl phthalate (DBP) were the two phthalates most prevalent in cosmetics.[3] DEP was found in 71 percent of all cosmetics tested, including deodorant, hair mousse, hair spray, and hand and body lotions; it was found in 100 percent of all fragrances and 86 percent of all hair gels. The fragrances carried the highest concentrations (in parts per million [ppm]) of DEP, with five products having 20,000-28,000 ppm of this plasticizer. DBP was also found in 67 percent of all nail polishes tested.

Mono-ethylhexyl phthalate (MEHP) is one of the metabolites of DEHP (previously known as di-n-octyl phthalate [DOP]), which is considered to be the most toxic phthalate.[4] MEHP was among the

Table 2. Urinary Levels of Phthalate Metabolites in Pregnant Women

Phthalate	Detection frequency	Geometric mean	50th percentile	75th percentile	95th percentile
Mono-benzyl phthalate	100%	8.9	7.5	16.8	95.8
Mono-isobutyl phthalate	100%	41.3	42.1	72.8	249
Mono-n-butyl phthalate	100%	43.2	42.7	86.6	197
Mono-ethyl phthalate	97%	112	117	425	1150
Mono-ethylhexyl phthalate	96%	6.9	6.9	17.3	82.8
Mono-(2-ethyl-5-hydroxyhexyl) phthalate	100%	14.3	14	30	86.2

lowest of the phthalate metabolites found in individuals in both studies, accounts for less than 10 percent of all DEHP metabolites, and has the shortest half-life. The major metabolites of DEHP are secondary oxidized metabolites with a half-life up to 24 hours and were only measured in the CDC study. These include mono-(2-ethyl-5-hydroxyhexyl) phthalate representing about 24 percent of DEHP, mono-(2-ethyl-5-oxyhexyl) phthalate accounting for about 15 percent of total DEHP, and mono-(2-ethyl-5-carboxypentyl) phthalate accounting for 18.5 percent of DEHP. While these comprise the majority of DEHP metabolites, they may also account for the majority of its toxicity, especially regarding developmental damage.[5] The primary environmental source of DEHP and DBP is the diet, rather than cosmetics or personal care products.[6]

DEHP leaches into foods from wrappings used for food storage and from PVC gloves worn by food handlers.[7] In a study of Korean and Japanese beverages, DEHP and di-methyl phthalate (DMP) were the two phthalates most frequently found and in highest concentrations.[8] The highest levels of these compounds were found in the beer, wine, and "nutritive drink" samples. According to data from the National Health and Nutrition Examination Survey (NHANES), poultry and eggs were the greatest sources of DEHP,[9] and tomatoes and potatoes were the highest sources of DEP; fruits contained DMP and fish contained DIBP.

theophylline.[10] In a German study, the other main source of phthalate exposure for individuals was house dust, with the two highest phthalates in dust being DEHP and DINP (but DEP and DBP were also present).[11]

Adverse Health Effects

The greatest concern about phthalates, known to have anti-androgenic activity, is regarding reproduction and human development. Various animal studies have demonstrated phthalates can reduce sperm counts, cause histological changes in the testes, and reduce male fertility. There are also concerns about phthalates causing fetal mortality, low birth weights, and fetal malformations.[4]

Although phthalates have not been shown to cause low birth weight in human studies,[12] they were associated with preterm deliveries.[13] In adult males, a combination of either MBP or monobenzyl phthalate (MBzP) (metabolites of di-butyl phthalate and di-benzyl phthalate, respectively) and PCBs was positively associated with reduced sperm motility.[14] The researchers noted that PCBs were able to inhibit the activity of glucuronyl transferase, thereby reducing the effective clearance of phthalates from the body. With these findings it appears that prolonging the exposure to either mono-butyl or mono-benzyl phthalate can lead to reduced sperm motility. Significantly, the participants in this study were all male partners of infertile couples who were seeking fertility help.

Table 3. Comparison of Phthalate Metabolite Levels in NHANES and in Cases of Male Infertility in the Hauser Study[15]

Metabolite	Geometric mean (ng/mL)	Frequency of detection	50th percentile		75th percentile		95th percentile	
			Hauser	NHANES	Hauser	NHANES	Hauser	NHANES
MEP	171	100%	154	153	513	452	2030	2040
MEHHP	55.9	>95%	48.6	17.7	111	35.8	601	182
MEOHP	21.4	>95%	32	12.1	71.3	24.3	444	118

Medications are another source of phthalate exposure. In a large study that utilized NHANES data, very high levels of mono-butyl phthalate (MBP) were found in persons taking mesalamine (approximately 100 times higher than non-mesalamine users), didanosine, omeprazole, and

Another study of men presenting at fertility clinics revealed a strongly significant association between DNA-damaged sperm and urinary levels of either mono-ethyl phthalate or the oxidative metabolites of DEHP (mono-[2-ethyl-5-hydroxyhexyl] phthalate [MEHHP] and mono-[2-ethyl-5-oxyhexyl]

phthalate [MEOHP]).[15] Interestingly, the levels of MEP in this group of infertile males were strikingly similar to those found in NHANES (Table 3), while the levels of MEHHP and MEOHP were much higher. This increased level of DEHP metabolites may reflect either a greater exposure or a metabolic defect. The sperm DNA damage was significantly correlated to all three metabolites individually, not just cumulatively. Thus, the presence of any of them at levels commonly found in the U.S. population can damage sperm.

Phthalates appear to cause more damage to male reproduction when the exposure occurs during male fetal development. Exposure to environmental endocrine disruptors during germ cell development appears to be the most opportune time for damage to occur. In an animal study, prenatal exposure to phthalates resulted in the male offspring developing testicular dysgenesis syndrome as a result of Leydig cell dysfunction.[16] *In vitro* experimentation with human fetal testes revealed that MEHP, the least toxic of the metabolites of DEHP, caused increased apoptosis of germ cells.[17] Because the researchers only used MEHP, it cannot be determined whether the more toxic metabolites of DEHP or other phthalate metabolites would have had similar or more powerful effects.

A study of mother-infant pairs showed a clear association between maternal levels of urinary phthalate metabolites (MEP, MBP, MBzP, MEHP) and reduced ano-genital distances in their offspring.[18] The ano-genital distance was measured in this study because it is a sensitive marker for *in utero* anti-androgen exposure. An association was also found between phthalate metabolite levels in maternal breast milk and sex hormone levels and ratios in male offspring.[19] MEP and MBP were positively associated with levels of sex-hormone binding globulin, while MEP was negatively correlated with free testosterone. Maternal phthalate exposure has also been positively associated with hypospadias in their offspring, which also reflects anti-androgenic effects during fetal sexual development.[20] Young girls with exposure to phthalates appear to have problems with premature sexual development, especially thelarche (premature breast development).[21,22]

Fetal exposure to maternal phthalate burden has also been associated with behavior and mental ability. Urine phthalate metabolites were tested in pregnant women in New York City during their third trimester and their offspring were first assessed within five days of birth[23] and again between ages four and nine years.[24] Within days after birth, children whose mothers had higher levels of phthalates exhibited more problems with alertness and orientation. Unfortunately, when they were tested again between the ages of four and nine, the neurological problems had persisted and even increased. Children with higher exposure to phthalates *in utero* had more problems with aggression, conduct, attention, and depression. They also exhibited poorer executive functioning and emotion control.

Other chronic health problems have also recently been associated with ongoing phthalate exposures. It was mentioned earlier that house dust is one of the sources of phthalate exposure. In a Swedish study, high levels of butylbenzyl phthalate (BBzP) in house dust were associated with higher rates of rhinitis and eczema, while dust-borne DEHP was associated with increased rates of asthma.[25] Along with asthma, other chronic health problems that are considered worldwide epidemics are obesity and type 2 diabetes, which are now being associated with phthalate exposure.[26] In a study utilizing NHANES data, urinary levels of MBzP, MEP, and the oxidative metabolites MEHHP and MEOHP were all associated with increased waist circumference in men.[27] The metabolites MBP, MBzP, and MEP were also associated with insulin resistance. A different study showed a positive association between MBzP at any level and body mass index (BMI).[28]

In women, MEP levels were positively correlated with both BMI and waist circumference. Women with higher levels of urinary MEHP also had higher rates of uterine leiomyomas, while those with higher levels of MBP had more endometriosis.[29] In addition, women with elevated MEHP and a glutathione transferase Mu 1 null genotype had odds ratios of 10.4 for adenomyosis and 5.9 for leiomyomas. Urinary MEP levels were also positively associated with increased rates of breast cancer.[30] Women with the highest levels of MEP were 2.2 times more likely to develop breast cancer than those with the lowest levels. For premenopausal women the odds ratio was even higher at 4.13. The mean MEP levels (mcg/g creatinine) were 169.6 for cases and 106.8 for controls, which are approximately the same as NHANES normal ranges. Thus, just as was found with infertility in males, the levels of phthalates that can lead to cancer were similar to the levels found in most U.S. residents.

Avoidance Measures

A dietary intervention study confirmed the role of foods as a major source of phthalate exposure. A group of 25 individuals participated in a five-day stay at a Buddhist temple in Korea and ate the vegetarian diet that was normally served to the resident monks.[31] Metabolites of four phthalates were found in all of the participants before their stay. Although all the metabolites dropped dramatically by the end of the stay, they did not disappear completely, as one might expect because of their short half-lives, indicating that not all sources of exposure (such as personal care products and medications) were eliminated by changing to vegetarianism. While this study does not state how the foods were purchased or prepared, an easy way to avoid phthalates in foods is to purchase foods that are not wrapped in plastic. In the book *Slow Death by Rubber Duck*,[32] the author conducted an experiment where he avoided all personal care products with phthalates for two days and then tested baseline phthalate levels, followed by two days of using classic personal care products and retesting. The levels of MEP went from 64 (after two days of avoidance) to 1,410 mg/mL after another two days of exposure. These two studies show that making dietary and lifestyle changes can either increase or decrease daily exposure to phthalates, and that proper avoidance may alter the risk of developing diseases associated with daily phthalate exposure.

Parabens

Methyl-, ethyl-, propyl-, butyl-, and benzyl parabens, all esters of p-hydroxybenzoic acid, are widely used as antimicrobial preservatives in cosmetics, pharmaceuticals, food, and beverages. Because of their low cost and low toxicity, they are used commonly throughout the world. Once in the bloodstream they can be conjugated in the liver with glycine, sulfate, or glucuronate for excretion in the urine. But, they are also lipophilic and can be absorbed through the skin and are found intact in tissue. In fact, these compounds have been found in breast cancer tissue in levels ranging from 20 ng/g tissue to 100 ng/g tissue.[33] Urinary levels of the parabens (ng/mL) from 100 U.S. residents are provided in Table 4.[34]

Parabens have weak estrogenic activity and have been shown to induce the growth of MCF-7 human breast cancer cells *in vitro*,[35] leading some researchers to suggest their potential as initiators or promoters of breast cancer. Part of the concern stems from the fact that an increasing number of breast cancers are occurring in the upper outer quadrant of the breast, where paraben-containing antiperspirant application occurs.[36] Others debate that the estrogenic effect is too weak to cause problems.[37] The current consensus is that parabens' effect on health, including cancer risk, is due to much more than estrogen mimicry.

An alternative mechanism by which parabens can indirectly affect estrogen levels is via inhibition of sulfotransferase activity inside the cytosol of human skin cells. By blocking sulfotransferases, the estrogen levels can remain higher than normal.[38] If this same action occurs in breast tissue, then these compounds may indeed be linked to increased rates of breast cancer.

Methyl- and propyl parabens, the two most commonly found, are also potent inhibitors of mitochondrial function.[39,40] This action alone would make them unwanted xenobiotics, especially for anyone with mitochondrial dysfunction-related health problems. This effect on mitochondrial function has been proposed as a mechanism for their possible role in male infertility.[41]

Table 4. Urinary Levels of Parabens (ng/mL) in 100 U.S. Residents

Paraben	Percent detection	50th percentile	75th percentile	90th percentile	95th percentile
Methyl	99	43.9	180	412	680
Ethyl	58	1.0	6.9	25.1	47.5
Propyl	96	9.1	49.2	144	279
Butyl	69	0.5	3.3	14.5	29.5
Benzyl	39	<LOD	0.2	0.4	0.5

LOD=level of detection

Conclusion

Phthalates are ubiquitous in foods, home dust, medications, and personal care products. Unless glucuronidation is inhibited, they are rapidly excreted by the body, making reductions in daily exposure readily apparent. Unfortunately, when exposed *in utero*, these compounds cause lasting health effects. In children of both genders phthalate exposure leads to increased rates of inattention and mood disorders as well as cognitive problems. In males exposure can cause reduced Leydig cell function, lower testosterone, hypospadias, and infertility. In young girls phthalates have been associated with premature sexual development, especially with early breast development. In adults phthalates are associated with increased weight, insulin resistance, asthma and allergies, uterine fibroids, and breast cancer.

The effects of phthalates are surprising and shocking considering they are supposedly safe and do not bioaccumulate. Testing for urinary phthalate metabolite levels provides a quick and easy means of identifying current exposure sources (that may not be as obvious as one would think). Avoidance of exposure through dietary changes, such as avoidance of foods packaged in plastic wrap, avoidance of fragrances and hair gels, and careful selection of personal care products (by using only those stating that they are phthalate- and paraben-free) can dramatically reduce one's daily exposure to these compounds. It is quite possible that such steps could help reduce the risk of asthma, allergies, diabetes, and breast cancer. Avoidance of phthalates may also dramatically improve the life-experience of unborn children by preventing neurological, reproductive, and endocrine disorders.

Paraben exposure comes mainly from the use of personal care products containing these compounds. While their exact health effects are currently unknown, they do possess some estrogenic activity, can adversely affect the breakdown of endogenous estrogens, and cause mitochondrial dysfunction. These compounds can be easily measured in the urine; testing can evaluate what exposures are occurring and monitor the effectiveness of avoidance procedures.

References

1. http://www.cdc.gov/exposurereport/ [Accessed March 19, 2010]
2. Ye X, Pierik FH, Hauser R, et al. Urinary metabolite concentrations of organophosphorous pesticides, bisphenol A, and phthalates among pregnant women in Rotterdam, the Netherlands: The Generation R Study. *Environ Res* 2008;108:260-267.
3. Houllhan J, Brody C, Schwan B. Not too pretty. Phthalates, beauty products & the FDA. http://www.ewg.org/files/nottoopretty_final.pdf [Accessed May 18, 2010]
4. Heudorf U, Mersch-Sundermann V, Angerer J. Phthalates: toxicology and exposure. *Int J Hyg Environ Health* 2007;210:623-634.
5. Stroheker T, Cabaton N, Nourdin G, et al. Evaluation of anti-androgenic activity of di-(2-ethylhexyl)phthalate. *Toxicology* 2005;208:115-121.
6. Fromme H, Gruber L, Schlummer M, et al. Intake of phthalates and di(2-ethylhexyl)adipate: results of the Integrated Exposure Assessment Survey based on duplicate diet samples and biomonitoring data. *Environ Int* 2007;33:1012-1020.
7. Tsumura Y, Ishimitsu S, Saito I, et al. Eleven phthalate esters and di(2-ethylhexyl) adipate in one-week duplicate diet samples obtained from hospitals and their estimated daily intake. *Food Addit Contam* 2001;18:449-460.
8. Yano K, Hirosawa N, Sakamoto Y, et al. Phthalate levels in beverages in Japan and Korea. *Bull Environ Contam Toxicol* 2002;68:463-469.
9. Colacino JA, Harris TR, Schecter A. Dietary intake is associated with phthalate body burden in a nationally representative sample. *Environ Health Perspect* 2010;118:998-1003. Doi:10.1289/ehp.0901712 http://dx.doi.org [Accessed April 14, 2010]
10. Hernandez-Diaz S, Mitchell AA, Kelley KE, et al. Medications as a potential source of exposure to phthalates in the U.S. population. *Environ Health Perspect* 2009;117:185-189.
11. Fromme H, Lahrz T, Piloty M, et al. Occurrence of phthalates and musk fragrances in indoor air and dust from apartments and kindergartens in Berlin (Gemany). *Indoor Air* 2004;14:188-195.
12. Wolff MS, Engel SM, Berkowitz GS, et al. Prenatal phenol and phthalate exposures and birth outcomes. *Environ Health Perspect* 2008;116:1092-1097.
13. Meeker JD, Hu H, Cantonwine DE, et al. Urinary phthalate metabolites in relation to preterm birth in Mexico City. *Environ Health Perspect* 2009;117:1587-1592.

14. Hauser R, Williams P, Altshul L, Calafat AM. Evidence of interaction between polychlorinated biphenyls and phthalates in relation to human sperm motility. *Environ Health Perspect* 2005;113:425-430.
15. Hauser R, Meeker JD, Singh NP, et al. DNA damage in human sperm is related to urinary levels of phthalate monoester and oxidative metabolites. *Hum Reprod* 2007;22:688-695.
16. Hu GX, Lian QQ, Ge RS, et al. Phthalate-induced testicular dysgenesis syndrome: Leydig cell influence. *Trends Endocrinol Metab* 2009;20:139-145.
17. Lambrot R, Muczynski V, Lecureuil C, et al. Phthalates impair germ cell development in the human fetal testis *in vitro* without change in testosterone production. *Environ Health Perspect* 2009;117:32-37.
18. Marsee K, Woodruff TJ, Axelrad DA, et al. Estimated daily phthalate exposures in a population of mothers of male infants exhibiting reduced anogenital distance. *Environ Health Perspect* 2006;114:805-809.
19. Main KM, Mortensen GK, Kaleva MM, et al. Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age. *Environ Health Perspect* 2006;114:270-276.
20. Nassar N, Abeywardana P, Barker A, Bower C. Parental occupational exposure to potential endocrine disrupting chemicals and risk of hypospadias in infants. *Occup Environ Med* 2009 Jun 24 [Epub ahead of print] Doi:10.1136/oem.2009.048272.
21. http://dx.doi.org [Accessed July 29, 2010]
22. Chou YY, Huang PC, Lee CC, et al. Phthalate exposure in girls during early puberty. *J Pediatr Endocrinol Metab* 2009;22:69-77.
23. Colon I, Caro D, Bourdony CJ, Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environ Health Perspect* 2000;108:895-900.
24. Engel SM, Zhu C, Berkowitz GS, et al. Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort. *Neurotoxicology* 2009;30:522-528.
25. Engel SM, Miodovnik A, Canfield RL, et al. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect* 2010;118:565-571.
26. Bornehag CG, Sundell J, Weschler CJ, et al. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. *Environ Health Perspect* 2004;112:1393-1397.
27. Sharp D. Environmental toxins, a potential risk factor for diabetes among Canadian aboriginals. *Int J Circumpolar Health* 2009;68:316-326.
28. Stahlhut RW, van Wijngaarden E, Dye TD, et al. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. *Environ Health Perspect* 2007;115:876-882.
29. Hatch EE, Nelson JW, Qureshi MM, et al. Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999-2002. *Environ Health* 2008;7:27. Doi:10.1186/1476-069X-7-27.
30. http://dx.doi.org [Accessed July 29, 2010]
31. Huang PC, Tsai EM, Li WF, et al. Association between phthalate exposure and glutathione S-transferase M1 polymorphism in adenomyosis, leiomyoma and endometriosis. *Hum Reprod* 2010;25:986-994.
32. Lopez-Carrillo L, Hernandez-Ramirez RU, Calafat AM, et al. Exposure to phthalates and breast cancer risk in Northern Mexico. *Environ Health Perspect* 2010;118:539-544.
33. Ji K, Lim Kho Y, Park Y, Choi K. Influence of a five-day vegetarian diet on urinary levels of antibiotics and phthalate metabolites: a pilot study with "Temple Stay" participants. *Environ Res* 2010;110:375-382.
34. Smith R, Lourie B, Dopp S. *Slow Death by Rubber Duck: How the Toxic Chemistry of Everyday Life Affects Our Health*. Mississauga, ON Canada: Knopf Canada; 2009.
35. Darbre PD, Aljarrah A, Miller WR, et al. Concentrations of parabens in human breast tumours. *J Appl Toxicol* 2004;24:5-13.
36. Ye X, Bishop AM, Reidy JA, et al. Parabens as urinary biomarkers of exposure in humans. *Environ Health Perspect* 2006;114:1843-1846.
37. Byford JR, Shaw LE, Drew MG, et al. Oestrogenic activity of parabens in MCF7 human breast cancer cells. *J Steroid Biochem Mol Biol* 2002;80:49-60.
38. Darbre PD, Harvey PW. Paraben esters: review of recent studies on endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. *J Appl Toxicol* 2008;28:561-578.
39. Golden R, Gandy J, Vollmer G. A review of the endocrine activity of parabens and implications for potential risks to human health. *Crit Rev Toxicol* 2005;35:435-458.
40. Prusakiewicz JJ, Harville HM, Zhang Y, et al. Parabens inhibit human skin estrogen sulfotransferase activity: possible link to paraben estrogenic effects. *Toxicology* 2007;232:248-256.
41. Soni MG, Taylor SL, Greenberg NA, Burdock GA. Evaluation of the health aspects of methyl paraben: a review of the published literature. *Food Chem Toxicol* 2002;40:1335-1373.
42. Soni MG, Burdock GA, Taylor SL, Greenberg NA. Safety assessment of propyl paraben: a review of the published literature. *Food Chem Toxicol* 2001;39:513-532.
43. Tavares RS, Martins FC, Oliveira PJ, et al. Parabens in male infertility – is there a mitochondrial connection? *Reprod Toxicol* 2009;27:1-7.