

Presence of phthalates in gastrointestinal medications: Is there a hidden danger?

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Abstract

Pharmaceutical companies that produce gastrointestinal (GI) medications often utilize phthalates for their ability to localize medication release. Commonly prescribed GI medications that may utilize phthalates are 5-Aminosalicylates, proton pump inhibitors, and pancreatic enzymes. Our understanding of the cumulative health effects of phthalates from medications remains unclear, and there is increasing evidence that phthalates are not harmless. Experimental studies in animals have shown that phthalates, specifically dibutyl phthalate and Di-(2-ethyl-hexyl) phthalate, have the potential to alter and/or inhibit reproductive biology and in utero development. Despite the lack of definitive human data, many cohort and cross-sectional studies demonstrate concerning associations between phthalates and poor health status, specifically developmental problems. Longitudinal studies and studies with larger sample sizes are required to determine whether phthalates actually cause negative health consequences. It is also important that physicians regularly review and discuss with patients the medicinal ingredients in their medications and supplements, specifically in pregnant woman with

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Key words: Phthalates; Dibutyl phthalate; 5-Aminosalicylates; Medications; Development; Pregnancy

Core tip: Phthalates are widely used as excipients in medications used to treat gastrointestinal disease. Research into the adverse effects associated with certain phthalates continues to produce uncertainty regarding the safety of their use in medications. Gastroenterologists should be aware of the potential harm of specific phthalates so that they can make informed decisions of whether the benefits of the medication outweigh the potential risks. Additional studies using human populations will help elucidate if regulatory bodies should mandate the use of alternative excipients.

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INTRODUCTION

Phthalates are plasticizers with widespread industrial use. Their unique chemical structure allows them to make plastic more flexible and durable^[1]. Phthalates are commonly used as softeners, solvents and additives, and are employed as excipients in gastrointestinal (GI) medications^[2-4]. Pharmaceutical companies that produce GI medications often utilize phthalates for their ability to localize medication release. More specifically, low molecular weight (LMW) phthalates are found in oral medications that require both controlled time release and location

sensitive release at certain points along the GI tract^[5]. Our understanding of the cumulative health effects of phthalates from medications remains unclear, and there is increasing evidence that phthalates are not harmless. This paper will review phthalate utilization in GI medications and summarize the evidence for the possible hidden danger of these common additives.

CHEMICAL STRUCTURE

Phthalates are diesters of 1,2-benzendicarboxylic acid (phthalic acid) and are present in both industrial and commercial synthetic products^[5]. Phthalate esters are prepared by the esterification of two moles of monohydric alcohol with one mole of phthalic anhydride^[6]. When used as an additive to industrial products, phthalates are often combined with polyvinyl chloride (PVC) because they are cheap and are able to provide important properties to plastics such as flexibility and durability. As a result, phthalates are found in more than 80% of the global plasticizer market^[6]. LMW phthalate subgroups have fewer than eight carbon atoms and include diethyl phthalate (DEP) and dibutyl phthalate (DBP), while high molecular weight (HMW) phthalates have eight or more carbon atoms in an alkyl chain^[7]. The commonly used HMW phthalate, Di-(2-ethyl-hexyl) phthalate (DEHP), is found in many products containing PVC^[7]. Most phthalates used as plasticizers have between 4 and 13 carbon atoms. These specific carbon lengths are used since fewer than four carbons can make compounds too volatile and more than 13 carbons are less effective at combining with PVC molecules^[6].

BIOABSORPTION

Since phthalates are the most widely used additives in plastics, their absorption in the body has been extensively studied. Phthalates do not bio-accumulate in the body. However, their widespread use translates into a large exposure in the general population^[8]. Phthalates are quickly metabolized to mono-alkyl metabolites and glucuronides and are excreted in both urine and feces^[9-12]. The urine content of phthalates and their metabolites have been shown to be sensitive biomarkers of phthalate intake. Therefore, urine screening has been used in many studies to assess phthalates levels in the population^[2,13,14]. Specifically, United States and German population data have shown widespread exposure to phthalates in urine samples^[5,14,15]. A United States study using data from the National Health and Nutrition Examination Survey found that over 75% of urinary samples contained some form of a phthalate metabolite, and it has been speculated that urine studies may underestimate phthalate levels in humans, as metabolites may be metabolized into undetectable byproducts^[2,14].

GI MEDICATIONS AND PHTHALATES

Scientists utilize various techniques to permit the release

of medication at specific parts of the luminal GI tract. For instance, using the prodrug technique, an inert drug is transformed into its active form at various pH levels. As an alternative method, the pharmaceutical industry has relied heavily on phthalates to assist with delivery of GI medications to precise areas of the luminal GI tract.

Compared to HMLW phthalates, LMW phthalates are more commonly used in pharmaceutical products. Phthalates used as excipients include cellulose acetate phthalate, DBP, DEP, dimethyl phthalate, hypromellose phthalate, and PVC^[16]. Excipients are defined as inactive ingredients found in medications that aid in the manufacturing, administration or absorption of the drug^[17]. They usually possess no active pharmacological ingredients and are regarded as inert. For example, LMW excipients such as DBP and DEP are listed in the FDA Inactive Ingredients Database for use in oral capsules, delayed action, enteric coated and controlled release tablets^[18]. Phthalates can also be combined with different polymers to maintain medication flexibility^[19]. This can assist with the localization of active ingredients through the delayed release of the inner components of solid drugs^[19,20].

An extensive review of pharmaceutical literature revealed that many GI medications contain phthalates as both excipients and inactive ingredients^[17]. For instance, this review found that mesalamine, pancreatic lipase, sulfasalazine, ranitidine and omeprazole are prescription drugs marketed in either Canada or the United States with labels that identified an ortho-phthalate as an inactive ingredient. The phthalate DBP, which has been shown to have potentially harmful adverse effects, is found in nonprescription medications such as bisacodyl and many probiotic supplements used frequently by gastroenterologists^[17]. Omeprazole and ranitidine contain the phthalate DEP, of which there is no evidence of potential harm.

The extensive use of phthalates in GI medications has prompted research into the cumulative effects of phthalates on those taking these drugs for prolonged periods of time. GI medications utilize phthalates more than most medications and are, therefore, more likely to result in high exposure to phthalates. Studies have shown that among patients prescribed, some of the aforementioned GI medications, specifically mesalamine and omeprazole, urine concentrations of phthalates have been documented at levels 100 times higher than the general population^[5]. It has also been shown that DBP and DEP, commonly used as excipients, can be found at concentrations of 9000 micrograms per capsule in some GI medications^[11]. These concentrations are concerning, as it has been shown that only 3600 micrograms per capsule can result in DBP metabolites in urine that are above the recommended tolerable daily intake^[11]. Well-designed retrospective studies are needed to determine the long-term effects of using GI medications with high levels of phthalates.

HARMFUL EFFECTS OF PHTHALATES

Experimental studies in animals have shown that phthal-

ates, specifically DBP and DEHP, have the potential to alter and/or inhibit reproductive biology and in utero development^[5]. One study demonstrated that mice exposed to 190 times the recommended amount of Asacol, a 5-ASA drug that contains DBP, were at risk for developing skeletal malformations and reproductive adverse effects^[21]. These concerns prompted additional studies which revealed that phthalates can act as anti-androgens and subsequently have toxic interactions with androgen receptors^[22,23]. Nonetheless, little data exists to help determine whether phthalates act as endocrine hormones at high levels in humans. Whether phthalates have meaningful interactions with proteins at the cellular level also remains unclear^[24,25].

Despite the lack of definitive human data, many cohort and cross-sectional studies demonstrate concerning associations between phthalates and poor health status, specifically developmental problems. For instance, a study in the United States found positive associations between LMW phthalate metabolites and several developmental indicators, including gestational age and head circumference. These results demonstrate that phthalates may potentially alter childhood development from birth^[26]. Research from Denmark showed a potentially detrimental correlation between phthalate monoesters and hormones essential for normal in utero development^[26,27]. Multi-center cohort studies from the United States and Mexico studying male children demonstrated that prenatal urinary phthalate concentration is negatively correlated with genital development, including anogenital distance, an index of demasculinization of the male reproductive tract, and penile width^[23,28,29]. Cross-sectional data from the United States, China, and Sweden comparing phthalates levels with semen concentration and semen quality have raised concern about deleterious interactions^[30-34]. By measuring phthalate metabolites in urine, dose-response relations have been found between some phthalate metabolites and sperm concentration, motility, and morphology^[30,32]. Despite the associations between phthalates and semen indices, this data has not been reproduced in the general population.

Additionally, phthalates have been associated with stunted neurodevelopment^[35,36]. A cross-sectional study from South Korea displayed a negative relationship between urinary concentration of phthalate metabolites and performance on various IQ tests^[35]. Moreover, United States cohort data indicated a positive association between maternal urine concentration of certain phthalates and increased negative behavior on validated behavior reporting tools^[36]. One cohort study from Denmark showed a negative association between phthalate metabolites in urine and normal serum levels of thyroid hormone^[37]. Interestingly, a cohort study from South Korea showed an association between phthalate metabolites in the urine, specifically DEHP, and increased attention deficit hyperactivity disorder symptoms^[38]. Recent research has provided conflicting data on the association of phthalates with the early onset of puberty and its associ-

ated symptoms^[22,39]. A case-control study from Turkey demonstrated an association between plasma levels of certain phthalates and gynecomastia, while a multicenter cohort study performed in the United States showed no association between phthalates concentration in the urine and precocious puberty^[22,39]. Finally, cross-sectional and cohort studies out of Sweden, Russia and Finland have implicated respiratory complications such as rhinitis and asthma with phthalates^[40-43]. However, the evidence for the association between phthalates and these clinical manifestations remains weak as most of these studies used PVC exposure as a proxy to phthalate exposure.

5-AMINOSALICYLATES

5-Aminosalicylates (5-ASAs) are used as first line therapy in treatment for mild to moderate ulcerative colitis (UC). Initial research in phthalate exposure and GI medications has focused on 5-ASAs users. Specifically, absorption data shows concerning levels of phthalates in the urine of chronic users of mesalamine, a 5-ASA drug. United States data demonstrated that six individuals taking mesalamine had metabolites of DBP 50-fold higher than those not using mesalamine^[10]. Similarly, one third of patients taking mesalamine had urine levels of phthalates that exceeded FDA recommended levels^[5,10]. While no equivocal evidence exists, gastroenterologists treating UC should consider prescribing 5-ASAs without DBP. This consideration should be especially taken in women of child-bearing age, as DBP may have deleterious effects during pregnancy based on animal studies.

Studies of pregnant and lactating women have shown that phthalates appear in maternal and umbilical blood, amniotic fluid and breast milk^[27,44-46]. As a result, women taking 5-ASA formulations have been evaluated for potential adverse effects during pregnancy^[47-50]. While no randomized control studies exist, a meta-analysis using 7 cohort studies did not indicate that woman taking 5-ASA during pregnancy have significantly higher rates of congenital abnormalities compared to control groups using no medication^[51]. Pooled odd ratios from these studies demonstrated 1.16, 2.38, 1.14, 1.35 and 0.93 fold increase in congenital malformations, still births, spontaneous abortions, preterm deliver and low birth weight, respectively^[51]. Based on this data, the 5-ASA formulation under the brand name of Asacol has been classified by the FDA as a pregnancy class C, which reflects adverse effects in animal but not human studies^[21]. As such, it is important that women taking 5-ASA drugs are informed about the potential risk of drugs containing DBP, especially when there are alternative 5-ASA formulations that do not contain DBP. Nonetheless, it must be emphasized that the risks of not taking 5-ASA while in remission far outweigh the benefits of avoiding phthalates. In addition, clinicians should consider 5-ASA formulations that release predominantly into the colon and do not contain phthalates. For example, Mezavant is a 5-ASA drug that uses an Multi Matrix system delayed release mechanism,

which allows release to be primarily in the colon where it can be most effective at treating ulcerative colitis. It has been shown to be equally efficacious at achieving IBD remission and does not contain phthalates in its coating^[52]. Salofalk is another alternative 5-ASA formulation available in Canada and utilizes pH-dependent release. Its Eudagrit-L coating, contains the DEP rather than DBP. Unlike the latter, DEP has not been shown to be harmful in animal studies.

REGULATION OF PHTHALATES

Throughout the previous decade, much of the media attention covering phthalates has targeted the presence of these plasticizers in children toys. Multiple agencies throughout the world have regulated phthalates in non-medical products including toys, cosmetics, environmental chemicals and health related products^[53-57].

Only recently has more attention been focused on phthalates in medications. In December 2012, the Center for Drug Evaluation and Research, a group affiliated with the FDA, recommended against the use of DBP and DEHP as excipients in prescription and nonprescription medications, and encouraged the use of alternative phthalates when possible^[20].

The FDA has likely limited their advice to recommendations since clinical and nonclinical research has only demonstrated an association between exposure to these phthalates and developmental problems, and there remains no evidence that medications with phthalates cause phenotypic physiologic abnormalities. These studies have been strictly correlational in nature, and thus a cause-effect relationship cannot be proven.

Accumulating pressure on pharmaceutical companies has encouraged the development of alternatives to phthalates. Pharmaceutical companies have developed excipients that do not contain phthalates. As mentioned, Salofalk and Mezavant are alternative 5-ASA formulations that contain alternative phthalates other than DBP or DEHP or a delayed release mechanism that does not incorporate phthalates^[52,58].

FUTURE DIRECTIONS FOR PHTHALATES

It is currently challenging to identify which medications contain phthalates, along with the specific dosage of phthalates included. Levels of phthalates for many medications are not openly displayed, due to proprietary formulations^[17]. Current standards do not require that inactive components are included on the package labeling of dietary supplements^[59]. It is the authors' opinion that government regulators should continue to advocate for the display of all components on drug packaging. It is also important that physicians regularly review and discuss with patients the medicinal ingredients in their medications and supplements. Patients should also be encouraged to use their pharmacists as a resource. Specifically, pregnant woman should review their medications

with pharmacists and discuss the potential presence of phthalates and possible alternatives. Of course, all these decisions should be made in conjunction with the advice of a physician.

Based on the empirical evidence available to date, government regulators and physicians must take caution against phthalates. Recommendations from government regulators should be followed if feasible and will hopefully facilitate the development and utilization of alternatives to phthalates. In order to further explore preliminary concerns, additional research with robust methodology should be conducted. Longitudinal studies capable of demonstrating causation are required to determine whether phthalates actually cause negative health consequences. Studies with larger sample sizes will also help quantify how much DBP and DEHP is being absorbed through specific medications. These studies might help with comparative quantification of bioabsorption between medication and environment (non-medical) exposures, which will help direct policy. Such research will permit government regulatory bodies, drug companies and doctors to respond appropriately.

REFERENCES

- 1 **University of Massachusetts Lowell.** Phthalates and their alternatives: Health and Environmental Concerns. Lowell: Lowell Center For Sustainable Production 2011; 31: 1-24
- 2 **Wormuth M, Scheringer M, Vollenweider M, Hungerbühler K.** What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? *Risk Anal* 2006; **26**: 803-824 [PMID: 16834635 DOI: 10.1111/j.1539-6924.2006.00770.x]
- 3 **ATSDR (Agency for Toxic Substances and Disease Registry).** Toxicological profile for Di (2-ethylhexyl) phthalate. Atlanta: US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry; 2002
- 4 **ATSDR (Agency for Toxic Substances and Disease Registry).** Toxicological profile for Di-N-Butyl phthalate. Atlanta: US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry; 2002
- 5 **Hernández-Díaz S, Mitchell AA, Kelley KE, Calafat AM, Hauser R.** Medications as a potential source of exposure to phthalates in the U.S. population. *Environ Health Perspect* 2009; **117**: 185-189 [PMID: 19270786 DOI: 10.1289/ehp.11766]
- 6 **Wilkes CE, Summers JW, Daniels CA, Berard MT.** PVC handbook. Cincinnati: Hanser Gardner Publications, 2005
- 7 **Calafat AM, Silva MJ, Reidy JA, Earl Gray L, Samandar E, Preau JL, Herbert AR, Needham LL.** Mono-(3-carboxypropyl) phthalate, a metabolite of di-n-octyl phthalate. *J Toxicol Environ Health A* 2006; **69**: 215-227 [PMID: 16263692 DOI: 10.1080/15287390500227381]
- 8 **Jurewicz J, Hanke W.** Exposure to phthalates: reproductive outcome and children health. A review of epidemiological studies. *Int J Occup Med Environ Health* 2011; **24**: 115-141 [PMID: 21594692 DOI: 10.2478/s13382-011-0022-2]
- 9 **Keller BO, Davidson AG, Innis SM.** Phthalate metabolites in urine of CF patients are associated with use of enteric-coated pancreatic enzymes. *Environ Toxicol Pharmacol* 2009; **27**: 424-427 [PMID: 21783974 DOI: 10.1016/j.etap.2008.12.005]
- 10 **Hauser R, Duty S, Godfrey-Bailey L, Calafat AM.** Medications as a source of human exposure to phthalates. *Environ Health Perspect* 2004; **112**: 751-753 [PMID: 15121520 DOI: 10.1289/ehp.6804]

- 11 **Seckin E**, Fromme H, Völkel W. Determination of total and free mono-n-butyl phthalate in human urine samples after medication of a di-n-butyl phthalate containing capsule. *Toxicol Lett* 2009; **188**: 33-37 [PMID: 19433267 DOI: 10.1016/j.toxlet.2009.03.002]
- 12 **Hauser R**, Calafat AM. Phthalates and human health. *Occup Environ Med* 2005; **62**: 806-818 [PMID: 16234408 DOI: 10.1136/oem.2004.017590]
- 13 **Fromme H**, Bolte G, Koch HM, Angerer J, Boehmer S, Drexler H, Mayer R, Liebl B. Occurrence and daily variation of phthalate metabolites in the urine of an adult population. *Int J Hyg Environ Health* 2007; **210**: 21-33 [PMID: 17182278 DOI: 10.1016/j.ijheh.2006.09.005]
- 14 **Silva MJ**, Barr DB, Reidy JA, Malek NA, Hodge CC, Caudill SP, Brock JW, Needham LL, Calafat AM. Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999-2000. *Environ Health Perspect* 2004; **112**: 331-338 [PMID: 14998749 DOI: 10.1289/ehp.6723]
- 15 **Becker K**, Seiwert M, Angerer J, Heger W, Koch HM, Nagorka R, Rosskamp E, Schlüter C, Seifert B, Ullrich D. DEHP metabolites in urine of children and DEHP in house dust. *Int J Hyg Environ Health* 2004; **207**: 409-417 [PMID: 15575555 DOI: 10.1078/1438-4639-00309]
- 16 **Rowe RC**, Sheskey PJ, Quinn M. Handbook of pharmaceutical excipients with CD-ROM. 2009
- 17 **Kelley KE**, Hernández-Díaz S, Chaplin EL, Hauser R, Mitchell AA. Identification of phthalates in medications and dietary supplement formulations in the United States and Canada. *Environ Health Perspect* 2012; **120**: 379-384 [PMID: 22169271 DOI: 10.1289/ehp.1103998]
- 18 **Crowley P**, Martini LG. Drug-excipient interactions. *Pharm Technol* 2001; **4**: 7-12
- 19 **Betts KS**. Phthalates in Prescription Drugs: Some Medications Deliver High Doses. *Environ Health Perspect* 2009; **117**: A74
- 20 Limiting the use of certain phthalates as excipients in CDER-regulated products [Internet]. 2012, cited 2013 March 23. Available from: URL: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM294086.pdf>
- 21 **Chilcott W**. Asacol full prescribing information [Internet]. 2010, cited 2013 March 23. Available from: URL: <http://www.asacolhd.com/pdfs/AsacolHDPrescribingInfo.pdf>
- 22 **Durmaz E**, Ozmert EN, Erkekoglu P, Giray B, Derman O, Hincal F, Yurdakök K. Plasma phthalate levels in pubertal gynecomastia. *Pediatrics* 2010; **125**: e122-e129 [PMID: 20008419 DOI: 10.1542/peds.2009-0724]
- 23 **Swan SH**. Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans. *Environ Res* 2008; **108**: 177-184 [PMID: 18949837 DOI: 10.1001/archpediatrics.2012.241]
- 24 **Nomura Y**, Mitsui N, Bhawal UK, Sawajiri M, Tooi O, Takahashi T, Okazaki M. Estrogenic activity of phthalate esters by in vitro VTG assay using primary-cultured Xenopus hepatocytes. *Dent Mater J* 2006; **25**: 533-537 [PMID: 17076324 DOI: 10.4012/dmj.25.533]
- 25 **Wolf C**, Lambright C, Mann P, Price M, Cooper RL, Ostby J, Gray LE. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. *Toxicol Ind Health* 1999; **15**: 94-118 [PMID: 10188194 DOI: 10.1177/074823379901500109]
- 26 **Wolff MS**, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, Wetmur J, Calafat AM. Prenatal phenol and phthalate exposures and birth outcomes. *Environ Health Perspect* 2008; **116**: 1092-1097 [PMID: 18709157 DOI: 10.1289/ehp.11007]
- 27 **Main KM**, Mortensen GK, Kaleva MM, Boisen KA, Damgaard IN, Chellakooty M, Schmidt IM, Suomi AM, Virtanen HE, Petersen DV, Andersson AM, Toppari J, Skakkebaek NE. 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 [PMID: 16451866 DOI: 10.1289/ehp.8075]
- 28 **Swan SH**, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, Mao CS, Redmon JB, Ternand CL, Sullivan S, Teague JL. Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ Health Perspect* 2005; **113**: 1056-1061 [PMID: 16079079 DOI: 10.1289/ehp.8100]
- 29 **Bustamante-Montes LP**, Hernández-Valero MA, Garcia-Fabila M, Halley-Castillo E, Karam-Calderon MA, Borja-Aburto VH. Prenatal phthalate exposure and decrease in ano-Genital distance in mexican male newborns. *Epidemiology* 2008; **19**: S270 [DOI: 10.1017/S2040174413000172]
- 30 **Duty SM**, Silva MJ, Barr DB, Brock JW, Ryan L, Chen Z, Herrick RF, Christiani DC, Hauser R. Phthalate exposure and human semen parameters. *Epidemiology* 2003; **14**: 269-277 [PMID: 12859026 DOI: 10.1097/01.EDE.0000059950.11836.16]
- 31 **Hauser R**, Meeker JD, Duty S, Silva MJ, Calafat AM. Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites. *Epidemiology* 2006; **17**: 682-691 [PMID: 17003688 DOI: 10.1097/01.ede.0000235996.89953.d7]
- 32 **Hauser R**, Meeker JD, Singh NP, Silva MJ, Ryan L, Duty S, Calafat AM. DNA damage in human sperm is related to urinary levels of phthalate monoester and oxidative metabolites. *Hum Reprod* 2007; **22**: 688-695 [PMID: 17090632 DOI: 10.1093/humrep/del428]
- 33 **Jönsson BA**, Richthoff J, Rylander L, Giwercman A, Hagmar L. Urinary phthalate metabolites and biomarkers of reproductive function in young men. *Epidemiology* 2005; **16**: 487-493 [PMID: 15951666 DOI: 10.1097/01.ede.0000164555.19041.01]
- 34 **Wirth JJ**, Rossano MG, Potter R, Puschek E, Daly DC, Paneth N, Krawetz SA, Protas BM, Diamond MP. A pilot study associating urinary concentrations of phthalate metabolites and semen quality. *Syst Biol Reprod Med*; **54**: 143-154 [PMID: 18570050 DOI: 10.1080/19396360802055921]
- 35 **Cho SC**, Bhang SY, Hong YC, Shin MS, Kim BN, Kim JW, Yoo HJ, Cho IH, Kim HW. Relationship between environmental phthalate exposure and the intelligence of school-age children. *Environ Health Perspect* 2010; **118**: 1027-1032 [PMID: 20194078 DOI: 10.1289/ehp.0901376]
- 36 **Engel SM**, Miodovnik A, Canfield RL, Zhu C, Silva MJ, Calafat AM, Wolff MS. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect* 2010; **118**: 565-571 [PMID: 20106747 DOI: 10.1289/ehp.0901470]
- 37 **Boas M**, Feldt-Rasmussen U, Skakkebaek NE, Main KM. Environmental chemicals and thyroid function. *Eur J Endocrinol* 2006; **154**: 599-611 [PMID: 16645005 DOI: 10.1530/eje.1.02128]
- 38 **Kim BN**, Cho SC, Kim Y, Shin MS, Yoo HJ, Kim JW, Yang YH, Kim HW, Bhang SY, Hong YC. Phthalates exposure and attention-deficit/hyperactivity disorder in school-age children. *Biol Psychiatry* 2009; **66**: 958-963 [PMID: 19748073 DOI: 10.1016/j.biopsych.2009.07.034]
- 39 **Lomenick JP**, Calafat AM, Melguizo Castro MS, Mier R, Stenger P, Foster MB, Wintergerst KA. Phthalate exposure and precocious puberty in females. *J Pediatr* 2010; **156**: 221-225 [PMID: 19892364 DOI: 10.1016/j.jpeds.2009.09.047]
- 40 **Larsson M**, Hägerhed-Engman L, Kolarik B, James P, Lundin F, Janson S, Sundell J, Bornehag CG. PVC--as flooring material--and its association with incident asthma in a Swedish child cohort study. *Indoor Air* 2010; **20**: 494-501 [PMID: 21070375 DOI: 10.1111/j.1600-0668.2010.00671.x]
- 41 **Bornehag CG**, Sundell J, Hagerhed-Engman L, Sigsggard T,

- Janson S, Aberg N. 'Dampness' at home and its association with airway, nose, and skin symptoms among 10,851 preschool children in Sweden: a cross-sectional study. *Indoor Air* 2005; **15** Suppl 10: 48-55 [PMID: 15926944 DOI: 10.1111/j.1600-0668.2005.00306.x]
- 42 **Jaakkola JJ**, Parise H, Kislitsin V, Lebedeva NI, Spengler JD. Asthma, wheezing, and allergies in Russian schoolchildren in relation to new surface materials in the home. *Am J Public Health* 2004; **94**: 560-562 [PMID: 15054004 DOI: 10.2105/AJPH.94.4.560]
- 43 **Jaakkola JJ**, Verkasalo PK, Jaakkola N. Plastic wall materials in the home and respiratory health in young children. *Am J Public Health* 2000; **90**: 797-799 [PMID: 10800434 DOI: 10.2105/AJPH.90.5.797]
- 44 **Huang PC**, Kuo PL, Chou YY, Lin SJ, Lee CC. Association between prenatal exposure to phthalates and the health of newborns. *Environ Int* 2009; **35**: 14-20 [PMID: 18640725 DOI: 10.1016/j.envint.2008.05.012]
- 45 **Högberg J**, Hanberg A, Berglund M, Skerfving S, Remberger M, Calafat AM, Filipsson AF, Jansson B, Johansson N, Appelgren M, Håkansson H. Phthalate diesters and their metabolites in human breast milk, blood or serum, and urine as biomarkers of exposure in vulnerable populations. *Environ Health Perspect* 2008; **116**: 334-339 [PMID: 18335100]
- 46 **Silva MJ**, Reidy JA, Herbert AR, Preau JL, Needham LL, Calafat AM. Detection of phthalate metabolites in human amniotic fluid. *Bull Environ Contam Toxicol* 2004; **72**: 1226-1231 [PMID: 15362453 DOI: 10.1007/s00128-004-0374-4]
- 47 **Diav-Citrin O**, Park YH, Veerasuntharam G, Polachek H, Bologa M, Pastuszak A, Koren G. The safety of mesalamine in human pregnancy: a prospective controlled cohort study. *Gastroenterology* 1998; **114**: 23-28 [PMID: 9428214 DOI: 10.1016/S0016-5085(98)70628-6]
- 48 **Nørgård B**, Fonager K, Pedersen L, Jacobsen BA, Sørensen HT. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. *Gut* 2003; **52**: 243-247 [PMID: 12524407 DOI: 10.1136/gut.52.2.243]
- 49 **Nørgård B**, Pedersen L, Christensen LA, Sørensen HT. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. *Am J Gastroenterol* 2007; **102**: 1406-1413 [PMID: 17437503 DOI: 10.1111/j.1572-0241.2007.01216.x]
- 50 **Moskovitz DN**, Bodian C, Chapman ML, Marion JF, Rubin PH, Scherl E, Present DH. The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patients. *Am J Gastroenterol* 2004; **99**: 656-661 [PMID: 15089898 DOI: 10.1111/j.1572-0241.2004.04140.x]
- 51 **Rahimi R**, Nikfar S, Rezaie A, Abdollahi M. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. *Reprod Toxicol* 2008; **25**: 271-275 [PMID: 18242053 DOI: 10.1016/j.reprotox.2007.11.010]
- 52 **Kamm MA**, Sandborn WJ, Gassull M, Schreiber S, Jackowski L, Butler T, Lyne A, Stephenson D, Palmes M, Joseph RE. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology* 2007; **132**: 66-75; quiz 432-3 [PMID: 17241860 DOI: 10.1053/j.gastro.2006.10.011]
- 53 Consumer product safety improvement act (CPSIA), section 108 [Internet]. 2008, cited 2013 Jan 25. Available from: URL: <http://www.cpsc.gov/cpsia.pdf>
- 54 Directive 2005/90/EC of the European Parliament and of the Council of 18 January 2006 amending, for the 29th time, Council Directive 76/769/EEC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations. *OJEU* 2006: Apr 2
- 55 **Robert B**. Toxicological review of dibutyl phthalate (Di-n-butyl phthalate) [Internet]. 2006, cited 2013 Jan 25. Available from: URL: http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=155707
- 56 DEHP in Plastic Medical Devices [Internet]. 2009, cited 2013 Jan 25. Available from: URL: <http://www.fda.gov/MedicalDevices/ResourcesforYou/Consumers/ChoosingaMedicalDevice/ucm142643.htm>
- 57 Order amending schedule I to the hazardous products act (Phthalates). Canada Gazette [Internet]. 2010; cited 2013 Jan 25; 144. Available from: URL: <http://gazette.gc.ca/rp-pr/p2/2010/2010-12-22/html/sor-dors297-eng.html#1>
- 58 **Nguyen GC**. Phthalates in 5-Aminosalicylates. *J Curr Clin Care* 2012; 14-21
- 59 **Consumer Health Products Associations**. The new over the counter medicine label [pamphlet]. New Jersey: Schering Plough, 2003

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