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Review

Developmental neurotoxicity of *ortho*-phthalate diesters: Review of human and experimental evidence

Amir Miodovnik [a,*], Andrea Edwards [b], David C. Bellinger [a], Russ Hauser [c,d]

[a] Boston Children's Hospital and Harvard Medical School, Boston, MA 02115, USA
[b] Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA
[c] Department of Environmental Health, Harvard School of Public Health, Boston, MA 02115, USA
[d] Vincent Obstetrics and Gynecology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02215, USA

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ABSTRACT

Ortho-phthalate diesters, or phthalates, are widely used synthetic chemicals found primarily in consumer products and polyvinyl chloride plastics. Experimental evidence suggests that several phthalates possess antiandrogenic properties and may disrupt endocrine pathways resulting in abnormal reproductive outcomes. Low-level exposure to phthalates has been well documented in humans, with higher levels found in children and women of childbearing age. Recent epidemiologic studies postulate that prenatal exposure to measurable urine phthalate concentrations may be associated with altered genital and pubertal development in infants and children. This review addresses the emerging evidence that some phthalates may have an adverse impact on the developing brain. The supporting animal studies and proposed mechanisms underlying the deleterious properties of phthalates in relation to neurodevelopmental outcomes are also discussed. While the observed associations are based on limited studies with a broad range of endpoints, the implications of such outcomes are of concern from a public health standpoint and merit further investigation given the widespread nature of the exposure.

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Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BASC-PRS, Behavior Assessment System for Children-Parent Rating Scales; BBP, butylbenzyl phthalate; BRIEF, Behavior Rating Inventory of Executive Function; BSID-II, Bayley Scales of Infant Development; CBCL, Childhood Behavior Checklist; CDC, centers for disease control and prevention; DBP, di-n-butyl phthalate; DCHP, dicyclohexyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DiBP, diisobutyl phthalate; DiDP, diisodecyl phthalate; DiHP, diisoheptyl phthalate; DMP, dimethyl phthalate; DOP, dioctyl phthalate; DnHP, di-n-hexyl phthalate; DnOP, di-n-octyl phthalate; GD, gestational day; MBzP, monobenzyl phthalate; MDI, Mental Development Index; MEP, monoethyl phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MiBP, mono-isobutyl phthalate; MMP, monomethyl phthalate; MnBP, mono-n-butyl phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; NIS, sodium/iodide symporter; NNNS, NICU Network Neurobehavioral Scale; PDI, Psychomotor Development Index; PND, postnatal day; PPARs, peroxisome proliferator-activated receptors; PSAI, Pre-School Activities Inventory; SRS, Social Responsiveness Scale; T4, thyroxine.

* Corresponding author at: Developmental Medicine Center, Boston Children's Hospital and Harvard Medical School, Boston, MA 02215, USA. Tel.: +1 617 355 7025; fax: +1 617 730 0252.
E-mail address: amir.miodovnik@childrens.harvard.edu (A. Miodovnik).

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1. Introduction

Phthalates are a high production volume group of synthetic chemical plasticizers and industrial solvents used to lend flexibility, durability, and solubility to materials ranging from flexible vinyl surfaces, PVC tubing, food packaging, medical equipment and children's toys to cosmetics, adhesives, insecticides and personal care products (Lyche et al., 2009); many of these products do not require labeling of phthalates as an ingredient (Dodson et al., 2012). There are over a dozen phthalates currently in commerce and six of the most commonly produced phthalates include di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DiNP), butylbenzyl phthalate (BBP or BBzP), diisoheptyl phthalate (DiHP), di-n-butyl phthalate (DBP or DnBP) and diethyl phthalate (DEP).

Mass production of phthalates began over 70 years ago, and currently more than 470 million pounds of phthalates are produced or imported into the US annually (EPA, 2006). Concern over human exposure has grown because phthalates are not covalently bound within the polymer matrix and, therefore, may leach or outgas into their surroundings. As a result, humans are regularly exposed to multiple phthalates through oral, dermal and inhalational routes and their metabolites have been detected in human saliva, urine, amniotic fluid and breast milk (Högberg et al., 2008; Silva et al., 2004b). National Health and Nutrition Examination Survey (NHANES) data have consistently demonstrated that the highest urine metabolite concentrations are found in children aged 6–12 years and women of reproductive age (Silva et al., 2004a).

Phthalates have primarily been studied for their anti-androgenic properties in relation to male reproductive tract development. Prenatal phthalate exposure has been associated with shortened anogenital distance, cryptorchidism and hypospadias in boys (Swan et al., 2005; National Research Council, 2008). These genital malformations may arise from phthalate-induced suppression of fetal gonadal testosterone synthesis (Wolff et al., 2008). Applying a similar conceptual model to the neuroendocrine system, phthalates may also disrupt hormone-sensitive aspects of brain development. This review examines the current body of evidence linking early phthalate exposure to aberrant child neurodevelopment (Table 1).

2. Epidemiologic studies and experimental correlates

2.1. Neonatal and infant neurological status

A prospective birth cohort study ($n = 295$) analyzed ten urinary metabolites of seven phthalate diesters in primiparous women collected between 25 weeks and 40 weeks gestation who went on to deliver at an urban hospital between 1998 and 2001 (Engel et al., 2009). Maternal metabolites were associated with scores on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) administered before hospital discharge. The BNBAS is an instrument used to assess neonatal adaptation to the extrauterine environment by measuring seven clusters of infant behavior as well as seven supplementary scales that pertain to the quality of the infant's performance. The behavioral items, including the supplementary items, were scored on a 9-point scale, with 1 being the worst and 9 being the best. To reduce the number of comparisons, phthalate metabolites were grouped into categories defined by molecular weight as high molecular weight phthalate (HMWP) metabolites (i.e., DEHP and BBP) or low molecular weight phthalate (LMWP) metabolites (i.e., DEP, DMP and DBP). Thus, 14 main outcomes were evaluated (seven NBAS clusters by 2 categories of phthalate metabolites).

There were no statistically significant associations for either LMWP or HMWP metabolites on any of the seven infant cluster scores. Because it was hypothesized that associations might be sex-specific, infant-sex phthalate interaction terms were evaluated. In sex-stratified analyses, girls showed a decline of 0.37 points on Orientation ($p = 0.02$) for each log-unit increase in micromolar concentration of HMWP, but no relationship was apparent in boys. To understand this finding, additional analyses were conducted using two of the supplementary scales considered to be relevant to an infant's ability to attend. For Quality of Alertness, girls' scores declined −0.48 (95% CI: −0.83, −0.12) for each log-unit increase in micromolar HMWP concentration. Boys showed slight improvement in scores on the Motor cluster (estimated beta coefficient = 0.09, $p = 0.01$, 95% CI not provided; estimated beta coefficient will hereafter be referred to as β) for each log-unit increase in micromolar concentration of LMWP.

Yolton et al. examined 350 mother–child dyads in which six urine phthalate metabolites were measured at 16 ± 4 weeks and 26 ± 4 weeks of gestation to reflect exposures during two distinct periods of pregnancy. The Pearson correlations of log-transformed urine phthalate metabolite concentrations across the two collection times were $r = 0.41$ ($p < 0.001$) for the sum of DBP metabolites and $r = 0.24$ ($p < 0.001$) for the sum of DEHP metabolites. Early infant neurobehavior was assessed using the NICU Network Neurobehavioral Scale (NNNS) at approximately 5 weeks after delivery. The NNNS evaluates neurological function and behavior and assesses signs of stress in young infants, yielding scores on 13 dimensions of behavior.

In multivariable analyses, no significant associations were found between metabolite concentrations measured at 16 weeks and any dimensions of infant behavior. Higher concentration of DBP metabolites at 26 weeks was significantly associated with improved arousal ($\beta = -0.072$, SE = 0.036, $p = 0.04$) and less need for handling ($\beta = -0.038$, SE = 0.016, $p = 0.02$). In addition, trends were evident indicating higher concentration of DBP metabolites were associated with improved self-regulation ($\beta = 0.080$, SE = 0.04, $p = 0.05$) and improved movement quality ($\beta = 0.054$, SE = 0.029, $p = 0.07$). Males showed more non-optimal reflexes with increasing concentration of DEHP metabolites ($\beta = 0.22$, SE = 0.09, $p = 0.02$). To provide a context for interpreting these effect sizes, the range of scores for arousal was 2.4–6; for need for handling, 0–1; for self-regulation, 2.9–7.5; for movement quality, 2.6–6.2, and for non-optimal reflexes, 0–9 (Yolton et al., 2011).

The clinical utility of a single neurological assessment during the neonatal or early infant period is uncertain and the long-term